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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 022009

Application Number: 09/445,517
Filing Date: 12/06/1999
Appellant: Duft *et al.*

For Appellant
Steven C. Koerber

EXAMINER'S ANSWER

This is in response to Appellant's brief on appeal filed 10/29/2008.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The Examiner is aware of a related pending appeal in application 08/870,762, of which the instant application is a continuation-in-part of, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement on the status of the claims contained in the brief is correct.

This appeal involves claims 23, 24, 27, 29, 31-34, 37-39, 68, 72, 76, 80, 82, 84 and 95-97.

Claims 1-22, 30, 40-67, 81 and 83 were previously canceled.

(4) Status of Amendment After-Final

The Appellant's statement of the status of the after-final amendment filed 05/12/08 contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of the claimed subject matter contained in the appeal brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The Appellants' statement of the grounds of rejection to be reviewed on appeal is correct.

Withdrawn Rejection

The following ground of rejection is not presented for review on appeal because the rejection has been withdrawn. The rejection of claim 80 made in paragraph 23 of the Office Action mailed 02/11/08 under 35 U.S.C § 112, first paragraph, as containing new matter, is withdrawn. Claim 80 depends from claim 23 and not from claim 33, and its inclusion in the rejection was inadvertent. The removal of claim 80 from the rejection statement does not alter the rejection.

Withdrawn Reference

The as-evidenced-by reference of Rink *et al.* (US 5,739,106) ('106), inadvertently included in the rejection of claims 23 and 33 made under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11 and 13 of US patent 5,321,008 issued to Beumont *et al.* ('008) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract), is hereby withdrawn. The rejection over Beumont *et al.* ('008) as evidenced by Tsanev however is maintained. The withdrawal of the citation of the '106 patent from the rejection does not alter the rejection of record.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The following evidence is relied upon by the Office in the rejection of the claims under appeal.

1) US patent 5,686,411 ('411) issued to Gaeta *et al.* and published 11/11/1997
2) Tsanev A. *Vutr. Boles*. 23: 12-17, 1994, original and English translation.
3) US patent 5,321,008 ('008) issued to Beumont *et al.* and published 06/14/1994
4) US patent 5,739,106 ('106) issued to Rink *et al.* and published 04/14/1998
5) WO 92/20367 of Rink *et al.* ('367), published 11/26/1992

6) US patent 5,364,841 ('841) issued to Cooper *et al.*, published 11/15/1994

7) US patent 5,280,014 ('014) issued to Cooper *et al.*, published 01/18/1994

8) Ratner *et al. Exp. Clin. Endocrinol. Diabetes* 113: 199-204, 2005 (Ratner, 2005)

9) Baron *et al. Current Drug Targets – Immune, Endocrine & Metabolic Disorders* 2: 63-82, 2002

10) US patent 5,175,145 ('145) issued to Cooper *et al.*, published 12/29/1992

11) WO 96/40220 ('220) of Kolterman *et al.*, published 12/19/1996

12) Kolterman *et al. Diabetologia* 39: 492-499, 1996 (Kolterman *et al.,* 1996)

13) Itasaka *et al. Psychiatr. Clin. Neurosci.* 54 : 340-341, 2000

14) Thompson *et al. Diabetes* 46: Suppl. 1, page 30A, 0116, May 02, 1997

15) Ratner *et al. Diabetes Technol. Ther.* 4: 51-61, 2002

16) Frishman *et al. In*: *Cardiovascular Pharmacotherapeutics*. (Eds) Frishman WH *et al.* McGraw-Hill Health Professions Division, New York, Chapter 48, pages 1093-1114, February 1997

17) Aronne *et al. Obesity* 14: A17, abstract 53-OR, 2006

18) Smith *et al. Diabetes* 56: A88, abstract 335-OR, 2007

19) Aronne *et al. J. Endocrinol. Metabol.* 92: 2977-2983, 2007

20) Smith *et al. J. Am. J. Physiol. Endocrinol. Metabol.* 293: E620-E627, 2007

21) US patent 6,114,304 issued to Kolterman *et al.*, published 09/05/2000

(9) Grounds of Rejections

The following grounds of rejections are applicable to the appealed claims.

Rejection(s) under 35 U.S.C § 112, First Paragraph (Scope of Enablement)

(A) Claims 23, 24, 27, 29, 31-34, 37-39, 68, 72, 76, 80, 82, 84 and 95-97 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a method of reducing the body weight of an insulin-taking type 2 diabetic human subject having a BMI of at least or less than 27 kg/m^2 comprising body weight not varying more than 45% from the desirable weight, by subcutaneous adjunctive administration to said subject, before each meal three times a day, an amount of the amylin agonist analogue species, ^{25,28,29}Pro-h-amylin (SEQ ID NO: 12), i.e.,

pramlintide, for 52 weeks, and a method of reducing body weight of an insulin-requiring human subject having type 1 diabetes mellitus having a BMI of at least or less than 27 kg/m^2 comprising subcutaneous adjunctive administration to said subject, before each meal four times, an amount of the amylin agonist analogue species, ^{25,28,29}Pro-h-amylin, i.e., pramlintide, for 20-52 weeks, wherein said pramlintide is not in conjunction with another obesity relief agent, wherein the body weight of said human subject is significantly reduced after 13, 26 and 52 weeks of said treatment compared to the body weight of the placebo group, does not reasonably provide enablement for a method of treating obesity in any human subject including a non-type 2 or non-type 1 diabetic human subject in need of treatment for obesity, or a type 1 or type 2 diabetic human subject in need of treatment for obesity who is *not* on insulin therapy, comprising or consisting of administering a generic amylin, a generic amylin agonist other than calcitonin or CGRP, or any amylin agonist or amylin agonist analogue other than pramlintide, or any peptide encompassed within the SEQ ID NO: 14 genus other than pramlintide, as claimed in a broad sense. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Instant claims are evaluated based on *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability in the art; and
- The breadth of the claims.

In the instant application, the nature of the invention is pertinent to treatment of obesity in a human subject in need of such treatment comprising or consisting of administering an amylin, an amylin agonist, or an amylin agonist analogue composition, or a peptide of SEQ ID NO: 14 in an amount effective to treat obesity in said subject. As described in the instant specification, the state of the art identifies obesity or adiposity as a 'chronic disease' that is highly prevalent in modern

society being strongly associated with multiple conditions including diabetes mellitus, insulin resistance, hypertension etc. The limitation 'obesity' encompasses diabetes-associated obesity, non-diabetes-associated obesity, morbid obesity, aging-associated obesity, insulin requiring obesity, obesity associated with family genetics, obesity due to hypernutrition etc. The breadth of the claimed method encompasses the following. The step recited in the independent claim 33 'consisting of' administering to a human subject in need of treatment for obesity, an amount of a composition comprising a pharmaceutically acceptable carrier and an obesity-relief agent consisting of an amylin or an amylin agonist (which includes an amylin agonist analogue) wherein the amount of said amylin or amylin agonist administered is about 0.01 mg to about 5 mg per day. A method of treatment 'consisting of' such an administration step *excludes* simultaneous insulin administration, or insulin administration minutes or hours before or after the administration. The method of treating obesity in a human subject in need of such treatment as claimed in the independent claim 23 'comprises' administering to said subject an amount of a composition comprising about 0.01 mg to about 5 mg per day of an amylin or an amylin agonist wherein said composition is not administered in conjunction with another obesity agent. The method of treating obesity in a human subject in need of treatment of obesity as claimed in the independent claim 76 and the dependent claim 68 'comprises' administering to said subject an amount of a composition 'comprising' an amylin agonist analogue or a peptide having an amino acid sequence of SEQ ID NO: 14, wherein A1 is Lys, Ala, Ser, or hydrogen; B1 is Ala, Ser or Thr; C1 is Val, Leu or Ile; D1 is His or Arg; E1 is Ser or Thr; F1 is Ser, Thr, Gln, or Asn; G1 is Asn, Gln or His; H1 is Phe, Leu or Tyr; I1 is Ile, Val, Ala or Leu; J1 is Ser, Pro or Thr; K1 is Asn, Asp or Gln; X and Y are independently selected residues having side chains which are chemically bonded to each other to form an intramolecular linkage, wherein said intramolecular linkage comprises a disulfide bond, a lactam or a thioether linkage; and Z is an amino, alkylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, alkyloxy, aryloxy or aralkyloxy; and provided that when A1 is Lys, B1 is Ala, C1 is Val, D1 is Arg, E1 is Ser, F1 is Ser, G1 is Asn, H1 is Leu, I1 is Val, J1 is Pro, and K1 is Asn; then one or more A to K1 is a D-amino acid and Z is selected from the group consisting of alkylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, alkyloxy, aryloxy or aralkyloxy, wherein the composition is not administered in conjunction with another obesity relief agent. Thus, the peptide

or the amylin agonist analogue administered in the method of these claims encompasses a huge genus comprising a huge number of the peptide or the amylin agonist analogue variant species each having the ability to treat obesity in a human in need thereof. In the method claimed in claim 76, the amount of the SEQ ID NO: 14 peptide administered is generic and is effective to treat obesity, whereas in claims 68 and 72, the amount of the amylin agonist analogue administered is about 0.01 mg to about 5 mg per day. A composition 'comprising' a pharmaceutically acceptable carrier and about 0.01 mg to about 5 mg per day of an amylin or an amylin agonist not administered in conjunction with another obesity agent includes any other element such as insulin, glucagon, an anti-diabetic agent, or a gastric emptying agent etc. The limitation 'a human subject in need of treatment for obesity' encompasses overweight, moderately obese, morbidly obese, diabetic and non-diabetic obese, insulin-requiring and insulin non-requiring obese human subject as well as a human subject with age-associated obesity. The limitations 'amylin agonist' and 'amylin agonist analogue' broadly encompass a myriad of compounds, including a peptide and a nonpeptide compound (see first two paragraphs on page 13 of the original specification), non-human amylins, amylins having amino acid modifications or substitutions, and the art-accepted amylin agonists such as calcitonin and CGRP (see lines 45-47 in column 7 of US patent 5,739,106 and claims 3 and 10 of US 5,175,145) etc. At least a representative number of the peptide species and the amylin agonist analogue species encompassed within the scope of the instantly claimed method is *required* to be effective in treating obesity in a diabetic or non-diabetic human subject, or a morbidly or non-morbidly obese human subject when administered in conjunction with or not in conjunction with another obesity relief agent in the recited amount or dose range.

With regard to the scope of enablement, a review of the instant specification indicates that Examples 4-10 are not enabling of the claimed method of treatment. Examples 4-6 describe how to prepare selective amylin agonist analogues. Therefore, whether or not peptide variants or amylin agonist analogues encompassed within the SEQ ID NO: 14 genus were known in the art at the time the present application was filed, and that such peptide variants or analogues included those described in US patent 5,686,411 as described in the present specification at page 13, lines 23-28 and those described in US 6,114,304, is not the issue. Example 7 of the instant specification pertains to the evaluation of *in vitro* binding of compounds to amylin receptors, whereas Example 8

pertains to the determination of amylin agonist activity of the compounds as measured by soleus muscle assay. Examples 9 and 10 describe methods of measuring gastric emptying using phenol red and tritiated glucose gastric emptying assays. However, what are claimed in the instant claims are not amylin agonist analogues or a method of making them, or using them in *in vitro* assays as described in Examples 4-10 of the instant specification, but a method of treating obesity in a human in need of treatment for obesity by administering *in vivo* an amount of an amylin, amylin agonist, amylin agonist analogue, or any peptide encompassed within the SEQ ID NO: 14 genus effective to treat obesity as claimed. Example 3 of the instant specification is limited to a demonstration that the human subjects of the study are those with a history of type 2 diabetes mellitus, who *required* insulin treatment. Body weight-wise, i.e., obesity-wise, these patients are described as having a BMI of at least 27.0 kg/m^2 or less than 27.0 kg/m^2 before admission into the study. The only amylin agonist analogue species or the peptide species that was administered in the instant invention was ^{25,28,29}Pro-h-amylin, also known as pramlintide. Groups of type 2 diabetic 'patients' were given separate mealtime pramlintide, 30 micrograms TID; 75 micrograms TID, or 150 micrograms TID subcutaneously, before each meal three times a day. Patients *remained on their insulin, usual diet, and exercise regimens*. The study period was 52 weeks, and the outcome was determined by comparing the mean body weight of the treated diabetic subjects with the mean body weight of the *placebo subjects*. See Tables V-VII. Thus, the originally filed specification at Example 3 and Tables V-VII describes a statistically significant reduction in the mean baseline body weight seen after the subcutaneous administration of specific amounts of one specific peptide or amylin agonist analogue species, pramlintide, three times a day, to type II diabetic subjects for 52 weeks, wherein said pramlintide administration was accompanied with *the continued use of insulin*. Example 2 of the instant specification is limited to a demonstration that the human subjects of the study are patients with a history of type 1 diabetes mellitus, who *required* insulin treatment. Body weight-wise, i.e., obesity-wise, these patients are described as having a BMI of at least 27.0 kg/m^2 before admission into the study. The only amylin agonist analogue species that was administered in the instant invention was ^{25,28,29}Pro-h-amylin, also known as pramlintide. Groups of type 1 diabetic patients were given subcutaneous *adjunctive* administration, before each meal four times a day, 30 micrograms of pramlintide for 20 weeks followed by either 30 or 60

micrograms of pramlintide QID up to week 52, of the amylin agonist ^{25,28,29}Pro-h-amylin, i.e., pramlintide. See Tables II-IV. Thus, the method comprised the administration insulin *and* the administration of a specific dose of pramlintide. The originally filed specification at Example 2 and Tables II-IV thus describes a statistically significant reduction in the mean baseline body weight seen after the subcutaneous administration of specific effective amounts of one specific amylin agonist analogue species, pramlintide, four times a day, to type I diabetic subjects for 52 weeks, wherein said pramlintide administration was accompanied with the *continued use of insulin*. However, this single enabled embodiment is not representative of the full scope of the claims which broadly encompasses the administration of any amylin, any amylin agonist, or any of a plethora of non-pramlintide amylin agonist analogues, including the multiple variants encompassed within the SEQ ID NO: 14 genus, in the treatment of obesity in diabetic and non-diabetic patients *not* on insulin treatment. This is critically important, because there was no predictability at the time of the invention that if one used an amylin, amylin agonist, or a non-pramlintide or non-calcitonin amylin agonist analogue in place of Applicants' pramlintide in type 2 diabetic or non-diabetic overweight or obese subjects who are on or not on insulin treatment, or morbidly obese human subjects who are on or not on insulin therapy, the administered amylin, amylin agonist, or non-pramlintide or non-calcitonin amylin agonist analogue would bring about significant or clinically meaningful obesity-treating effect. Neither the state of the art *at the time of the invention*, nor the instant specification as originally filed, provides specific guidance and direction with regard to the use of a generic amylin, or a non-pramlintide or non-calcitonin amylin agonist, or a non-pramlintide amylin agonist analogue including any variant of SEQ ID NO: 14 as recited, to treat obesity in any human subject in need of treatment for obesity.

Upon consideration of the evidence as a whole and analysis of all of the *Wands* factors, the instantly claimed method is viewed as being non-enabled with regard to the full scope. It should be noted that the scope of the required enablement varies inversely with the degree of predictability involved. A single embodiment may provide broad enablement in cases involving predictable factors. However, in applications directed to inventions in arts where results are unpredictable, the disclosure of a single species does not provide an adequate basis to support generic claims. MPEP § 2164.03. In cases involving unpredictable factors, such as most chemical

reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In the instant case for example, it is not obvious from the disclosure of the administration of pramlintide species in the treatment of obesity in type 2 or 1 diabetic humans, what other non-pramlintide amylin agonist analogues or SEQ ID NO: 14 peptide variant species would work in treating obesity in diabetic or non-diabetic humans in need of treatment for obesity. It should be noted that predictability or unpredictability is one of the *Wands* factors to be considered for enablement or lack thereof under 35 U.S.C § 112, first paragraph. The instantly claimed invention is in an area of art that is unpredictable. Amylin, and a sufficient number of non-pramlintide peptide or amylin agonist analogues, are not enabled as obesity relief agents in the instantly claimed method.

A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, *unless* there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). In the instant case, one of the reasons for doubting the objective truth of the statements comes from Appellants' own statement. For example, with regard to the state of the art at the time of the invention, Appellants have previously gone on the record with the following (see pages 9, 13 and 14 of Appellants' Appeal Brief filed July 2000 in the parent application 08/870,762) [Emphasis in original]:

> .... THE RINK PATENT PROVIDES THAT AMYLIN AND AMYLIN AGONISTS ADMINISTERED AS DESCRIBED AND CLAIMED IN THE PRESENT APPLICATION HAVE "NO MEASURABLE EFFECT" ON FOOD INTAKE.

> .... the Rink patent reports that a 1.0 μg/kg dose (**equivalent to about 70μg/dose in an adult human**) had no effect on food intake. [Emphasis in bold added]

The Rink patent that is being referred to by Appellants in the Appeal Brief is US 5,739,106. Note that the above-mentioned about 70 μg/dose in an adult human is encompassed within the therapeutic amount range of about 0.01 to about 5 mg, as recited in the instant claims 23 and 33. Appellants have not advanced any arguments with regard to this issue raised in the previous Office Action mailed 04/23/07. Thus, in view of the above-cited acknowledgment of the failure of amylin to have any effect on food intake, one of skill in the art would look into Applicants' specification for guidance and direction. However, the instant specification fails to show that human or non-human amylin, or a composition comprising or consisting of the same, was in fact stable, soluble and/or non-aggregating enough to be 'therapeutic' in a method of treating obesity upon administration in any amount and by any route, with or without concurrent insulin therapy, to a diabetic or non-diabetic human subject in need of treatment for obesity. With regard to the therapeutic use of amylin, the state of the art indicates the difficulty, the undesirable pharmacological properties, *and* the impracticability of using amylin, including human amylin, clinically as 'a therapeutic agent'. For instance, Baron *et al.* (*Current Drug Targets – Immune, Endocrine & Metabolic Disorders* 2(1): 63-82, 2002) taught the following with regard to the clinical use of amylin as a therapeutic agent:

> Clinical use of amylin as a therapeutic agent is considered impractical because of its instability in solution and its propensity to aggregate and adhere to surfaces, properties that hamper the manufacturing, formulation, and storage of this peptide as a drug. Pramlintide is a synthetic, equipotent analogue of human amylin in which the undesirable pharmacological properties of human amylin (insolubility, tendency to self-aggregate) have been overcome by replacement of the three amino acid residues .... with prolines ....

Ratner *et al.* (*Diabetes Technol. Ther.* 4: 51-61, 2002) provide a similar teaching (see paragraph bridging the two columns on page 52):

> Native human amylin is not ideal for clinical use because of the peptide's poor solubility and propensity to aggregate.

Applicants state that Baron *et al.* and Ratner *et al.* support enablement of the claimed invention (see page 28 of Applicants' amendment filed 10/23/07), but fail to explain how these references enable a method of administering amylin or any non-pramlintide amylin agonist analogue to a human for treating obesity.

Appellants have previously acknowledged that obesity is a complex, chronic, multifactorial disease that has been the subject of decades of research. Appellants have acknowledged that there are contradictions and confusion in the relevant art. See pages 22 and 23 of Applicants' response filed 09/02/04. Although Example 9 of the instant specification describes the gastric emptying assay and the effect of specific amounts of 'amylin' (as opposed to the amylin agonist analogue, SEQ ID NO: 14) on gastric emptying in diabetic rats, and Examples 7 and 8 describe the receptor binding and soleus assays of some amylin variants, of the various biologic activities or functions attributed to amylin or pramlintide, which precise activity or activities provide for, or are associated with obesity relief in the 'human subject' genus, has not been precisely identified. Of the various screenable activities, whether one activity, all the activities, or a specific combination of activities, are responsible for the obesity-relief function(s) is neither known in the art nor has it been established within the instant specification, absent which one of skill in the art cannot practice the claimed invention without engaging in a considerable amount of undue experimentation. A mere screening of art-known amylin agonist analogue species falling within the genus of SEQ ID NO: 14 using the conventional screening assays does not enable one to reproducibly practice the claimed method of treatment. Whether or not the various amylin agonist analogue species or peptide variant species encompassed within the scope of the SEQ ID NO: 14 genus have the *required* obesity relief function(s) is neither known nor can it be predicted. While there is no requirement for Applicants to enable all of the peptide variant species or amylin agonist analogue species encompassed within the claimed invention, enablement of a reasonable number such species in the claimed method is required particularly in view of the unpredictability. Applicants have previously stated that neither the amylin art nor the obesity art suggested or indicated an approach to trying an amylin or an amylin agonist (let alone an amylin agonist analogue or the peptide variant) for weight reduction or treatment of obesity. See bottom of page 57 of Applicants' response filed 09/02/04. With regard to what was known in the art at the time of the invention or thereafter, Applicants stated that Frishman *et al.* (*In*: *Cardiovascular Pharmacotherapeutics*. (Eds) Frishman WH *et al.* McGraw-Hill Health Professions Division, New York, Chapter 48, pages 1093-1114, February 1997) 'only' concluded that 'the potential role of amylin in weight reduction "awaits clinical investigation"'. See the full paragraph on page 85 of

Applicants' response filed 09/02/04. Thus, Applicants themselves have recognized the importance of the unpredictability previously. For example, with regard to the gastric emptying function/activity and obesity, Applicants have previously taken the position that there is no agreement on the effect of gastric emptying in obesity. Applicants pointed to various reports and stated that the role of gastric emptying in obesity was uncertain and controversial at the time of filing of the instant application, as well as before and after. See page 37 of Applicants' response filed 09/02/04. Applicants mentioned of a non-submitted Minnesota Medical Association's recent reporting (*Minnesota Medicine*, volume 83, November 2000) that gastric emptying is useful in treating diabetics, but that researchers are 'uncertain' whether it will produce weight loss. See page 37 of Applicants' response filed 09/02/04. Applicants have gone on the record previously stating that any and all compounds having gastric emptying activity are *not* necessarily useful for treating obesity, let alone one that is being evaluated for use in the treatment of diabetes. See lines 4-6 on page 85 of Applicants' response filed 09/02/04. With the art-known fact that obesity is a complex, chronic and multifactorial disease, and with the precise amylin or pramlintide activity contributing to obesity relief being unknown at the time of the invention, there is no predictability that the broadly recited peptide variants or amylin agonist analogues having the recited amino acid substitutions or chemical modifications, that are encompassed within the genus of SEQ ID NO: 14, would be therapeutically functional as effective obesity-relief agents in a human subject in need of treatment for obesity. Furthermore, the effects the various amino acid substitutions and/or chemical modifications would have on the activity of amylin agonist analogues or peptides contributing to the reported undesired side effects, including recurrent nausea, vomiting and excessive anorexia, and the undesired properties such as insolubility and tendency toward aggregation, are also unpredictable. The various amino acid substitutions and/or chemical modifications encompassed within the SEQ ID NO: 14 genus can potentially render the amylin agonist analogue species or peptide variant species more insoluble and aggregating than amylin and unacceptably nausea- or vomiting-inducing with no effect on food intake or obesity. In sum, the instant specification simply lacks a concrete *in vivo* showing that a representative number of amylin agonist analogue species or peptide species encompassed within the SEQ ID NO: 14 genus has obesity-relieving function in any human subject in need of treatment for obesity.

With regard to the quantity of experimentation needed, the standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: 'is the experimentation needed to practice the invention undue or unreasonable'. That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In the instant case, no guidance or direction has been provided in the instant specification so that one could predict which of the amylin agonist analogue species other than pramlintide or which of the peptide variant species of claim 76 other than pramlintide would have the requisite therapeutic effect against obesity. Because there is no way to predict *a priori* which amylin agonist analogues or peptides from the specification or the chemical structures alone would be therapeutically active against obesity in diabetic or non-diabetic humans subjects, including morbidly obese human subjects, an extraordinary amount of trial and error experimentation is required to identify the obesity-treating amylin agonist analogues or the peptides. Assuming *arguendo* that the experimentation required is routine, if one of skill in the art screens innumerable non-pramlintide amylin agonist analogue species or the peptide variant species currently encompassed within the recited genus, including those disclosed in Examples 4-6 of the instant invention, using receptor binding assays and assays for amylin activity, there is absolutely no predictability that a non-pramlintide amylin agonist analogue or peptide variant mimicking an effect of amylin would have obesity-treating effect, or food intake-reducing effect, given the Applicants' admission that amylin itself has no effect on food intake. Given this and the lack of showing within the instant specification, the obesity-treating effect of any amylin or any non-pramlintide or non-calcitonin amylin agonist analogue or peptide variant having amylin activity, administered alone or as an adjunct to insulin therapy, to an obese diabetic or obese non-diabetic human subject, is simply not predictable. Applicants have provided no guidance with regard to the use of extraordinarily large genus of amylins, amylin agonists, amylin agonist analogues, and peptides in the treatment of obesity in humans. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states: 'The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art'. The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly

how to make or *use* the invention. The more is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling' (MPEP 2164.03). MPEP also states that physiological activity can be considered inherently unpredictable. Whether the specification would have been enabling *as of the filing date* involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art. The state of the prior art is what one skilled in the art would have known, *at the time the application was filed*, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains *at the time the application was filed*. See MPEP § 2164.05(b). The *post-filing* abstracts of Aronne *et al*. (*Obesity* 14: A17, 2006) and Smith *et al*. (*Diabetes* 56: A88, 2007) submitted by Applicants are silent about the diabetic or non-diabetic status of the subjects included in the study. Both are limited to the use of the single amylin agonist analogue species, pramlintide, in the method described therein. The *post-filing* teachings of Aronne *et al*. (*J. Endocrinol. Metabol*. 92: 2977-2983, 2007) and Smith *et al*. (*J. Am. J. Physiol. Endocrinol. Metabol*. 293: E620-E627, 2007) submitted by Applicants are also limited to the use of one amylin agonist analogue species, pramlintide, for reducing caloric intake and meal size, or for reducing body weight. These two post-filing publications support the Office's position on the lack of enablement of the full scope of the instant claims by confirming that *even about a decade after the effective filing date of the instant application*, the only amylin agonist analogue species within the recited broad genus that is being used for inducing weight loss in humans is pramlintide. None of these post-filing references and abstracts represents the state of the art *at the time of filing*. Contrary to Applicants' allegation, a *prima facie* case of lack of scope of enablement has been established by providing sufficient references and specific technical reasons along with the documentation of Applicants' own previous statement indicating that an

amylin, amylin agonist, or amylin agonist analogue having an amylin activity does not necessarily have an effect on food or caloric intake, and therefore does not necessarily have an anti-obesity effect. Thus, in view of level of skill, the state of the art at the time of the invention, and the information in the specification, one of skill would *not* expect that the recited broad genus could be used in that manner without undue experimentation. For the reasons delineated above and due to the lack of specific direction or guidance within the instant specification, the breadth of the claims, the absence of working examples enabling the full scope, the art-recognized unpredictability factor, and the quantity of the experimentation necessary, a considerable amount of non-routine undue experimentation would have been required to reproducibly practice the full scope of the invention, as claimed. Instant claims do not meet the scope of enablement provisions of 35 U.S.C. § 112, first paragraph. The scope of enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the instant claims.

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(B) Claim 33 and the dependent claims 34, 37-39, 72, 82 and 96 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 33, as amended, includes the new limitations: treat obesity in said human subject …. wherein said human subject is in need of treatment for obesity …. method of treating obesity …. *consisting* of administering' [Emphasis added]. A method of treatment of obesity 'consisting of' such an administration step *excludes,* for example, simultaneous insulin administration, or insulin administration minutes or hours before or after the administration. However, neither the original claims, nor the description of the methods of treatment of the instant invention support such a method of treating obesity 'consisting of' administering an amount of a composition effective to

treat obesity in said human subject comprising an obesity relief agent consisting of an amylin or an amylin agonist and a pharmaceutically acceptable carrier. For example, the originally filed specification at lines 10-13 of page 12 of the specification states [Emphasis added]:

> The present invention is directed to novel methods for treating or preventing obesity in humans *comprising* the administration of an amylin or an amylin agonist, the amylin agonist analogue ^{25,28,29}Pro-human amylin.

Pages 28-29 and Table I describe a statistically significant reduction in the mean baseline weight seen after the subcutaneous administration of 60 micrograms TID or 60 micrograms QID of one specific amylin agonist analogue species, pramlintide, to type II diabetic subjects for four weeks, wherein said pramlintide administration was accompanied *with the continued administration of insulin*. The method of treatment of obesity as described in the originally filed specification comprised insulin treatment ***and*** the administration of a specific dose of pramlintide to type II diabetic patients. This however does not provide descriptive support for the now claimed method of treating obesity in a human in need of treatment for obesity, said method 'consisting' of administering to said subject an amount of a composition as recited comprising an amylin or any amylin agonist and a pharmaceutically acceptable carrier, wherein said amount of the composition is effective to treat obesity in said subject. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P. 608.04 to 608.04(c).

Rejection(s) under 35 U.S.C § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> **(e)** the invention was described in-
> **(2)** a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

(C) Claims 23, 24, 27, 29, 31, 33, 34, 37-39, 80 and 82 are rejected under 35 U.S.C § 102(b) as being anticipated by Kolterman *et al.* (WO 96/40220) ('220) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984).

It is noted that the limitation 'treating obesity' is defined in the instant specification as including 'controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance', or preventing 'the onset of symptoms or complications, alleviating the symptoms or complications'. See last paragraph on page 12 of the specification. It is further noted that the patient population used in the instant invention to treat obesity by the administration of the recited amount of pramlintide is insulin-requiring Type 2 diabetics. See Example 1 of the instant specification.

Kolterman *et al.* ('220) taught a method of administering to insulin-taking type II diabetic human subjects a dose of 10, 30, 50, 60 or 150 micrograms per day (i.e., the amount falling in the range recited in the instant claims) of the amylin agonist composition, pramlintide or $^{25, 28, 29}$pro-h-amylin, also known as AC137, i.e., the same amylin agonist administered in Examples 1 and 3 of the instant invention. The composition consisted of pramlintide and a pharmaceutically acceptable carrier, and was administered in single or multiple doses, for example, of about 30 micrograms QID, or about 60 micrograms TID or QID, i.e., an amount effective to treat obesity. See pages 9-11; paragraph bridging pages 20 and 21; page 21; first paragraph on page 19; lines 8-10 on page 19; and the first row reciting 'Insulin-Treated Patients' in each Table of Kolterman *et al.* ('220). Pramlintide was administered subcutaneously 1-4 times a day, before meals. See pages 9 and 22. Kolterman *et al.* ('220) additionally taught that the presence of obesity is a characteristic of 'most patients with Type II diabetes mellitus'. See page 10. Kolterman *et al.* ('220) taught the benefit of obtaining weight loss in Type II diabetic patients by teaching that hyperglycemia associated with Type II diabetes can be reversed or ameliorated by *weight loss* sufficient to restore the sensitivity of the peripheral tissues to insulin (see pages 7, first paragraph), thus teaching that Type II diabetic patients are indeed in need of treatment for obesity or weight loss. Thus, the very active step of the instantly claimed method was disclosed and practiced by Kolterman *et al.* ('220) in 1996 in the very same patient population, i.e., a human type II diabetes mellitus patients used by Applicants in Example 1 of the instant application. The prior art method is the *same* as the instantly claimed method with regard to the pramlintide amylin agonist or the amylin agonist analogue, the amylin agonist composition or the pramlintide amylin

agonist analogue composition administered, and the insulin-taking Type II diabetic patients used (80-90% of Type II diabetic patients being known in the art to be intrinsically obese as taught by Tsanev - see Tsanev's English abstract), the subcutaneous route of the administration used, the dose and the daily frequency of the amylin agonist pramlintide administered, and the administration step prior to meals. Given Tsanev's express disclosure that 80 to 90% of type II diabetic patients are intrinsically obese, and given Kolterman's ('220) recognition that obesity is an intrinsic characteristic of most patients with Type II diabetes mellitus and the indication that these patients are in need of weight loss, Kolterman's ('220) method of subcutaneous administration of pramlintide to Type II diabetic patients in an amount that falls within the range recited in the instant claims, necessarily serves as the claimed method of treating obesity, and therefore anticipates the instantly claimed method. Since 80-90% of Type II diabetic patients are known in the art to be intrinsically obese, 80-90% of Kolterman's ('220) type II diabetic patients to whom pramlintide composition was administered, necessarily qualify as human subjects in need of treatment of obesity as recited in the instant claims. The Office's position that Kolterman's ('220) method is the same as the Applicants' claimed method is based upon the fact that the method step, the pramlintide compound administered, the amount of the compound administered, the route by which the compound is administered, and the intrinsically obese diabetic human patient species to which the pramlintide compound was administered, are the *same* in the two methods. The art-recognized intrinsic obesity being prevalent in 80 to 90% of diabetic patients as disclosed by Tsanev (see Tsanev's English abstract), Kolterman's ('220) method of administration of the above-identified therapeutically effective amount (i.e., about 30 micrograms QID, or about 60 micrograms TID or QID, or a dose of 10, 30, 50, 60 or 150 micrograms per day) of the amylin agonist ^{25,28,29}Pro-human amylin to intrinsically obese type 2 diabetic human subject species anticipates the instant claims. Given that the method step of the Kolterman's ('220) method and the instant claims are the same, Kolterman's ('220) method is expected to bring about obesity-treating effect, weight gain-inhibiting or weight loss-causing therapeutic effect in the intrinsically obese pramlintide-treated type II diabetic patients. The obesity-relief, weight gain inhibition, or weight loss-induction is an inherent property inseparable from the administered pramlintide.

Claims 23, 24, 27, 29, 31, 33, 34, 37-39, 80 and 82 are anticipated by Kolterman *et al.* ('220). The publication of Tsanev is **not** used as a secondary reference in combination with the reference of

Kolterman *et al.* ('220), but rather is used to show that every element of the claimed subject matter is disclosed by Kolterman *et al.* ('220), with the unrecited limitation(s) being inherent as evidenced by the state of the art. See *In re Samour* 197 USPQ 1 (CCPA 1978). 'To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). See MPEP 2124. Tsanev's extrinsic evidence makes clear that the missing descriptive matter, i.e., 80 to 90% prevalence of obesity in Kolterman's ('220) diabetic subject species administered with pramlintide, is necessarily present in the method thing described by Kolterman *et al.* ('220). The method of Kolterman *et al.* ('220) clearly anticipates the claimed method of the instant invention, because Kolterman *et al.* ('220) taught the very step of the instantly claimed method in the very same human patient population species. The alleged failure of Kolterman ('220) to expressly mention treatment of obesity as a goal is irrelevant. To the extent the method embodiment in the claimed invention achieves treatment of obesity, so does the method of Kolterman's ('220). Where the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results. See *Mehl/Biophile International Corp. v. Milgraum*, U.S. Court of Appeals Federal Court, 52 USPQ2d 1303 and 1306, 192 F3d 1362, 1999 citing *W.L. Gore & Assocs. v. Garlack, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983). Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the disclosure of Kolterman *et al.* ('220), Kolterman's ('220) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the obesity-treating effect, weight gain-inhibiting effect, or weight loss-inducing effect. The obesity-relief or weight loss-induction is an inherent property inseparable from the administered pramlintide. The two structurally identical pramlintide compounds administered in the two methods (i.e., the prior art method

and the instant method) cannot have mutually exclusive properties. The same two methods cannot have mutually exclusive results.

(D) Claims 23, 24, 27, 29, 31, 33, 34, 37-39, 80 and 82 are rejected under 35 U.S.C § 102(b) as being anticipated by Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996) (Kolterman *et al.*, 1996) as evidenced by Itasaka *et al.* (*Psychiatr. Clin. Neurosci.* 54: 340-341, June 2000).

It is noted that the human patient in need of the recited treatment according to the instant invention is expressly identified in the instant specification as one having a body weight of 79 kg. A 70 kg patient is *not* excluded from the scope of the instant invention 'as a human subject in need thereof', but is expressly included. The recited therapeutic amount range of 'about 0.1 milligrams per day to about 1 milligram per day', or 'about 0.01 to about 5 mg/day', or 0.03 to about 5 mg/day of the amylin agonist or amylin agonist analogue, pramlintide, administered is specifically "for a 70 kg patient". See last paragraph of page 27 of the specification. A diabetic human patient having a baseline BMI of up to 27.0 kg/m^2 is not excluded from the scope of the instant invention 'as a human subject in need thereof', but is expressly included. See lines 25 and 26 of page 35 of the instant specification.

It is further noted that the claimed method of treating obesity in a human subject in need thereof encompasses alleviating the 'symptoms' of the disorder, i.e., obesity. See the last paragraph on page 12 of the instant specification. The substitute specification at paragraph bridging pages 10 and 11 characterizes 'increased appetite' as a sign strongly associated with obesity. Thus, increased appetite and therefore, increased food intake is viewed as a 'symptom' of obesity. It is further noted that the limitation 'treating obesity' is defined in the instant specification as including 'controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance', or preventing 'the onset of symptoms or complications, alleviating the symptoms or complications'. See last paragraph on page 12 of the instant specification.

Kolterman *et al.* (1996) taught a method of subcutaneous administration of 30, 100, or 300 μg of pramlintide composition or AC137 (i.e., $^{25, 28, 29}$pro-h-amylin, the same one used in Appellants' Example 2), a human amylin analogue, to human patients with insulin-dependent diabetes mellitus or IDDM who were on insulin. Pramlintide was administered three times daily for a period of 14 days. See abstract; and page 493. The mean body weight ± SEM of diabetic patients included in Kolterman's (1996) method who were administered subcutaneously with 30 micrograms, 100 micrograms, and 300

micrograms of pramlintide, three times a day for 14 days, was 70.6 $\pm$ 2.7, 74.4 $\pm$ 2.5, and 75.7 $\pm$ 2.6 respectively. Therefore, the 70.6 to 75.7 kg insulin-taking diabetic patients from Kolterman's (1996) study qualify as human subjects in need of treatment for obesity as recited in the instant claims. Additionally, even BMI-wise, Kolterman's (1996) diabetic subjects meet the limitation 'a human subject .... in need of treatment for obesity' as recited in the instant claims, because the diabetic subjects included in Kolterman's method (1996) had a BMI of up to 27. See second full paragraph under 'Subjects, materials and methods'. Therefore, Kolterman's (1996) diabetic subjects having a BMI at least in the range of 24 up to 27 do qualify as diabetic subjects in need of treatment for obesity in light of what is known in the art. For example, Itasaka *et al*. teach that a BMI of 24.0 to 26.4 represents mild obesity and 26.4 and heavier (i.e., including a BMI of 26.4 to 27) represents obesity in humans. See abstract of Itasaka *et al*. Kolterman's (1996) pramlintide composition did not comprise another obesity relief agent, but consisted of pramlintide. The pramlintide composition was injected subcutaneously to the human patients (see 'Study design') and therefore is expected to inherently contain a pharmaceutically acceptable carrier therein. The amount administered was 30 micrograms or 100 micrograms three times a day, or 300 micrograms per day. See 'Study design'; Table 1; and paragraph there below. Kolterman's (1996) subcutaneous administration of a therapeutically effective amount of the amylin agonist, pramlintide, to diabetic human subject species taking insulin and weighing 70 kg or more, or having a BMI falling in the BMI range of 24 up to 27, anticipates the claims drawn to Appellants' method of treating obesity in human subject genus in need thereof, as claimed currently. Thus, the very active step recited in the instantly claimed method was disclosed and practiced by Kolterman *et al*. in April, 1996. Given that the method step in Kolterman's (1996) method and the instant claims are the *same*, and the amylin agonist analogue pramlintide administered and its amount administered are the *same*, Kolterman's (1996) method is expected to necessarily bring about the same obesity-treating, weight gain-inhibiting (i.e., maintaining of existing body weight), or weight loss-inducing therapeutic effect in Kolterman's (1996) pramlintide-treated diabetic patient species who are on insulin. Since the prior art clearly taught the claimed method, any assertions of specific functional properties attributed to the amylin agonist pramlintide administered in the claimed method are merely inherent and do not necessarily make the claimed method patentable. The prior art method of administering the above-explained amount of the amylin agonist ^{25,28,29}Pro-human amylin (the same

pramlintide administered in Appellants' Example 2) to insulin-taking diabetic human subject species weighing 70 kg or more, and/or having a BMI falling in the range of 24 up to 27 necessarily serves as the Applicants' method of treating obesity by inhibiting weight gain or inducing weight loss, as claimed currently.

Claims 23, 24, 27, 29, 31, 33, 34, 37-39, 80 and 82 are anticipated by Kolterman *et al.* (1996). The publication of Itasaka *et al.* is **not** used as a secondary reference in combination with the reference of Kolterman *et al.* (1996), but rather is used to show that every element of the claimed subject matter is disclosed by Kolterman *et al.* (1996) with the unrecited limitation(s) being inherent as evidenced by the state of the art. See *In re Samour* 197 USPQ 1 (CCPA 1978). 'To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). See MPEP 2124. Itasaka's extrinsic evidence makes clear that the missing descriptive matter, i.e., prevalence of obesity in 80 to 90% Kolterman's (1996) insulin-taking diabetic subject species administered with ^{25,28,29}Pro-human amylin, is necessarily present in the method thing described by Kolterman *et al.* (1996). The method of Kolterman *et al.* (1996) clearly anticipates the claimed method of the instant invention, because Kolterman *et al.* (1996) taught the very step of the instantly claimed method in diabetic human patient species. The alleged failure of Kolterman *et al.* (1996) to expressly mention treatment of obesity as a goal is irrelevant. To the extent the method embodiment in the claimed invention achieves treatment of obesity, so does the method of Kolterman *et al.* (1996). Where the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results. See *Mehl/Biophile International Corp. v. Milgraum*, U.S. Court of Appeals Federal Court, 52 USPQ2d 1303 and 1306, 192 F3d 1362, 1999 citing *W.L. Gore & Assocs. v. Garlack, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983).

(E) Claims 23, 24, 29, 33, 34 and 38 are rejected under 35 U.S.C § 102(e)(2) as being anticipated by Gaeta *et al.* (US 5,686,411) ('411) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984).

The limitation 'method … comprising ….. wherein said compound is not administered in conjunction with another obesity relief agent' in claim 23, and the limitation 'composition comprising an obesity relief agent …. carrier' in claim 33 do not exclude the presence of an anti-diabetic agent, insulin, glucagon, a gastric emptying-inhibiting agent, etc. in the recited composition.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 C.F.R 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention 'by another', or by an appropriate showing under 37 C.F.R 1.131.

Gaeta *et al.* ('411) taught a method of treatment of diabetes mellitus in a mammal, including a patient seen by a medical practitioner, i.e., a human, comprising the administration to said mammal (human) of a therapeutically effective amount of the amylin agonist of claim 19, ^{25,28,29}Pro-human amylin (pramlintide). See claims 34, 35 and 19; and lines 45-53 in column 7 of the '411 patent. Gaeta *et al.* ('411) taught the 'therapeutically effective amount' of the amylin agonist to include the dosage units of 0.1 to 5 mg or 0.5 to 1.0 mg of the amylin agonist. See lines 53-59 in column 8. The amount effective to treat obesity encompassed in the instant claims as described in the instant application, for example, about 0.01 milligrams to about 5 milligrams per day, about 0.05 milligrams to about 2 milligrams per day, or 300 micrograms per dose, falls in the range of therapeutically effective amount of the amylin agonist disclosed in the '411 patent. Lines 9-14 of column 3 of the U.S. patent '411 describe that the limitation 'diabetes mellitus' includes insulin-requiring diabetes mellitus and that the administration is of amylin agonist analogue *alone*. The amylin agonist composition comprises a pharmaceutical carrier and the amylin agonist without insulin or glucagon. See lines 9-11 in column 7 and lines 37-39 in column 8. Given the art-known prevalence of intrinsic obesity in 80% to 90% of diabetic patients as disclosed by Tsanev (see abstract), the diabetic patient administered with the amylin agonist ^{25,28,29}Pro-human amylin in the method disclosed by the '411 patent qualifies a man patient in need of treatment for obesity. Given that the method step of the '411 patent and the instant claims are the *same*, the amylin agonist, ^{25,28,29}Pro-human amylin, administered and the amount administered are

the *same*, the method of the '411 patent is expected to bring about an obesity-treating therapeutic effect, weight gain-inhibiting effect, and weight loss-inducing effect in the intrinsically obese ^{25,28,29}Pro-human amylin-treated insulin-requiring diabetic patient of Gaeta ('411) as defined in the instant invention. Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the teachings of the '411 patent, Gaeta's ('411) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the obesity-treating effect, weight gain-inhibiting effect, or weight loss-inducing effect. The Office's position that Gaeta's ('411) method is the same as the Applicants' claimed method is based upon the fact that the method step, the amylin agonist, ^{25,28,29}Pro-human amylin administered, the amount of the ^{25,28,29}Pro-human amylin administered, and the intrinsically obese diabetic human patient species to whom the ^{25,28,29}Pro-human amylin is administered, are the *same* in the two methods. The art-recognized intrinsic obesity being prevalent in 80 to 90% of diabetic patients as disclosed by Tsanev (see English abstract), Gaeta's ('411) method of administration of the above-identified therapeutically effective amount (i.e., 0.1 to 5 mg, or 0.5 to 1.0 mg) of the amylin agonist ^{25,28,29}Pro-human amylin to intrinsically obese type 2 diabetic human subject species anticipates the instant claims. Given that the method step of the Gaeta's ('411) method and the instant claims are the *same*, Gaeta's ('411) method is expected to bring about the obesity-treating effect, weight gain-inhibiting, or weight loss-causing effect, against the intrinsic obesity in the ^{25,28,29}Pro-human amylin-treated, insulin-requiring human diabetic patient species. Since the prior art clearly taught the instantly claimed method, any assertions of specific functional properties attributed to the amylin agonist ^{25,28,29}Pro-human amylin in the claimed method are merely inherent and do not necessarily make the claimed method patentable.

Claims 23, 24, 29, 33, 34 and 38 are anticipated by Gaeta *et al.* ('411). The publication of Tsanev is **not** used as a secondary reference in combination with the reference of Gaeta *et al.* ('411), but rather is used to show that every element of the claimed subject matter is disclosed by Gaeta *et al.* ('411) with the unrecited limitation(s) being inherent as evidenced by the state of the art. See *In re Samour* 197 USPQ 1 (CCPA 1978). 'To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v.*

Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). See MPEP 2124. Tsanev's extrinsic evidence makes clear that the missing descriptive matter, i.e., prevalence of obesity in Gaeta's ('411) insulin-requiring diabetic subjects administered with ^{25,28,29}Pro-human amylin, is necessarily present in the thing described by Gaeta *et al.* ('411). The method of Gaeta *et al.* ('411) clearly anticipates the claimed method of the instant invention, because Gaeta *et al.* ('411) taught the very step of the instantly claimed method in the very same diabetic human patient species. The alleged failure of Gaeta *et al.* ('411) to expressly mention treatment of obesity as a goal is irrelevant. To the extent the method embodiment in the claimed invention achieves treatment of obesity, so does the method of Gaeta *et al.* ('411). Where the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results. See *Mehl/Biophile International Corp. v. Milgraum*, U.S. Court of Appeals Federal Court, 52 USPQ2d 1303 and 1306, 192 F3d 1362, 1999 citing *W.L. Gore & Assocs. v. Garlack, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983).

(F) Claims 23, 24, 27, 29, 33, 34, 37 and 38 are rejected under 35 U.S.C § 102(e)(2) as being anticipated by Beumont *et al.* (US 5,321,008) ('008) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984).

It is noted that the limitation 'method … comprising ….. wherein said compound is not administered in conjunction with another obesity relief agent' in claim 23, and the limitation 'composition comprising an obesity relief agent …. carrier' in claim 33 do not exclude the presence of an anti-diabetic agent, insulin, glucagon, a gastric emptying-inhibiting agent, etc. in the recited composition. It is further noted that 'amylin agonist' is defined in the instant specification as a peptide or non-peptide compound that mimics the effect of amylin. See third paragraph of the specification under 'Summary of the Invention'. Calcitonin and CGRP are described in the instant specification as sharing the food intake-suppressing action or effect of peripherally or centrally administered amylin. See first full paragraph on page 9 of the instant specification.

The applied reference has a common assignee with the instant application. Based upon the earlier

effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 C.F.R 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention 'by another', or by an appropriate showing under 37 C.F.R 1.131.

Beumont *et al.* ('008) taught a method of subcutaneous administration to an insulin-requiring human who suffers from Type 1 or Type 2 diabetes mellitus a therapeutically effective amount of an amylin agonist *alone* such as calcitonin, or calcitonin and insulin, contained in a pharmaceutically acceptable carrier. See claims 11, 7, 13 and 4; lines 14-17 in column 5; lines 8-11 and 49-54 in column 12; and lines 34 and 35 in column 2. Claim 11 of the '008 patent is directed to the method of administering a therapeutically effective amount of the amylin agonist calcitonin to an insulin-requiring human with diabetes mellitus. The 'therapeutically effective amount' taught by Beumont *et al.* ('008) includes the typical dosage units of about 0.1 to 1 mg of calcitonin. See first full paragraph in column 13. The amount effective to treat obesity, the amount effective to inhibit weight gain, or the amount effective to induce weight loss encompassed in the instant claims as described in the instant application of about 0.01 milligrams to about 5 milligrams per day, about 0.05 milligrams to about 2 milligrams per day, or 300 micrograms per dose, falls within the range of the therapeutically effective amount disclosed in the '008 patent. Given the art-known prevalence of intrinsic obesity in 80% to 90% of diabetic patients as disclosed by Tsanev (see English abstract), the diabetic patient used in the method disclosed in the '008 patent qualifies as a human patient in need of treatment for obesity. Therefore, the method of the '008 patent comprising the administration of about 0.1 to 1 mg of calcitonin to a diabetic human species anticipates the instant claims. Given that the method step of the '008 patent and the instant claims is the *same*, and the amylin agonist administered and the amount administered are the *same* as the ones described in the instant specification, the method of the '008 patent is expected to bring about an obesity-treating effect, weight gain-inhibiting effect, or weight loss-inducing effect in Beumont's intrinsically obese calcitonin-treated diabetic patient as defined in the instant invention. Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the teachings of the '008 patent, Beumont's ('008) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the obesity-treating effect, weight gain inhibiting effect, or weight loss-inducing effect. The Office's

position that Beumont's ('008) method is the same as the Applicants' claimed method is based upon the fact that the method step, the amylin agonist calcitonin administered and its amount administered, the subcutaneous route by which the amylin agonist is administered, and the intrinsically obese diabetic human patient species to which the amylin agonist is administered, are the *same* in the two methods. The art-recognized intrinsic obesity being prevalent in 80 to 90% of diabetic patients as disclosed by Tsanev (see English abstract), Beumont's ('008) method of administration of the above-identified therapeutically effective amount (i.e., dosage units of about 0.1 to 1 mg) of the amylin agonist calcitonin to the intrinsically obese type 2 diabetic human subject species anticipates the instant claims. Since the prior art clearly taught the instantly claimed method, any assertions of specific functional properties attributed to the amylin agonist calcitonin in the claimed method are merely inherent and do not necessarily make the claimed method patentable.

Claims 23, 24, 27, 29, 33, 34, 37 and 38 are anticipated by Beumont *et al.* ('008). The publication of Tsanev is **not** used as a secondary reference in combination with the reference of Beumont *et al.* ('008), but rather is used to show that every element of the claimed subject matter is disclosed by Beumont *et al.* ('008) with the unrecited limitation(s) being inherent as evidenced by the state of the art. See *In re Samour* 197 USPQ 1 (CCPA 1978). 'To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). See MPEP 2124. Tsanev's extrinsic evidence makes clear that the missing descriptive matter, i.e., prevalence of obesity in Beumont's insulin-requiring diabetic subject species administered with calcitonin, is necessarily present in the thing described by Beumont *et al.* ('008). The method of Beumont *et al.* ('008) clearly anticipates the claimed method of the instant invention, because Beumont *et al.* ('008) taught the very step of the instantly claimed method in the very same diabetic human patient species. The alleged failure of Beumont *et al.* ('008) to expressly

mention treatment of obesity as a goal is irrelevant. To the extent the method embodiment in the claimed invention achieves treatment of obesity, so does the method of Beumont *et al.* ('008). Where the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results. See *Mehl/Biophile International Corp. v. Milgraum*, U.S. Court of Appeals Federal Court, 52 USPQ2d 1303 and 1306, 192 F3d 1362, 1999 citing *W.L. Gore & Assocs. v. Garlack, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983).

Double Patenting Rejections

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970) and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R 3.73(b).

(G) Claims 23, 24, 33 and 34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 34 and 35 of the US patent 5,686,411 issued to Gaeta *et al.* ('411) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984).

The method of treatment claimed in claims 34 and 35 of the '411 patent includes administering to a mammal with diabetes mellitus a therapeutically effective amount of the amylin agonist of claim 19, ^{25,28,29}Pro-human amylin (pramlintide). The portion of the disclosure of the '411 patent at lines 45-53 in column 7 supporting the limitation 'mammal' does not exclude, but expressly includes a patient seen by a medical practitioner, i.e., a human. The portion of the disclosure of the '411 patent at second

paragraph under 'Summary of the Invention' supporting the limitations 'diabetes mellitus' and 'administration of .... an amylin agonist analogue' include *insulin-requiring* diabetes mellitus and administration of an amylin agonist analogue alone (i.e., consisting of) or in conjunction with insulin or a glucagon, i.e., not in conjunction with another obesity relief agent. The portion of the disclosure of the '411 patent at lines 53-59 in column 8 supporting the limitation 'therapeutically effective amount' of the amylin agonist includes the dosage units of 0.1 to 5 mg or 0.5 to 1.0 mg of the amylin agonist. The amount effective to treat obesity, encompassed in the instant claims as described in the instant application of about 0.01 milligrams to about 5 milligrams per day, or 300 micrograms per dose, falls within the range disclosed in the '411 patent. Given the art-known prevalence of intrinsic obesity in 80% to 90% of the *insulin-requiring* diabetic patients as disclosed by Tsanev (see English abstract) , 80% to 90% of the human diabetic patients used in the method disclosed in the '411 patent qualify as human patients in need of treatment for obesity. Therefore, the method of the '411 patent comprising or consisting of the administration of 0.1 to 5 mg, or 0.5 to 1.0 mg of the amylin agonist, ^{25,28,29}Pro-human amylin alone or in conjunction with insulin or glucagon, to diabetic human species anticipates the instant claims. Given that the method step of the '411 patent and the instant claims are the same, the amylin agonist analogue pramlintide used and its amount administered are the same, and the human diabetic patient used is the same, the method of the '411 patent is expected to bring about obesity-treating effect in the intrinsically obesity diabetic patient species administered with a therapeutically effective amount of the pramlintide as claimed in the instant invention. Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the disclosure of Gaeta *et al.* ('411), Gaeta's ('411) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the obesity-treating effect.

(H) Claims 23 and 33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11 and 13 of the US patent 5,321,008 issued to Beumont *et al.* ('008) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984).

The method of treatment claimed in claims 11 and 13 of the '008 patent includes administering to a human with type 2 diabetes mellitus a therapeutically effective amount of the amylin agonist, calcitonin. The portion of the disclosure of the '008 patent at lines 14-17 in column 5; lines 8-11 and 49-54 in column 12; and lines 34 and 35 in column 2 that supports the claims includes subcutaneous

administration to an insulin-requiring human who suffers from Type 1 or Type 2 diabetes mellitus a therapeutically effective amount of an amylin agonist *alone* such as calcitonin (i.e., consisting of), or calcitonin and insulin (i.e., comprising) contained in a pharmaceutically acceptable carrier. The portion of the disclosure of the '008 patent at first full paragraph in column 13 of the '008 patent supporting the 'therapeutically effective amount' includes the typical dosage units of about 0.1 to 1 mg of calcitonin. The amount effective to treat obesity, or the amount effective to treat obesity encompassed in the instant claims as described in the instant application, for example, about 0.01 milligrams to about 5 milligrams per day, about 0.05 milligrams to about 2 milligrams per day, or 300 micrograms per dose, falls within the range of the therapeutically effective amount disclosed in the '008 patent. Given the art-known prevalence of intrinsic obesity in 80% to 90% of diabetic patients as disclosed by Tsanev (see English abstract), 80 to 90% of *insulin-requiring* human diabetic patients used in the method in the above-identified of the '008 patent qualify as human patients in need of treatment for obesity. Therefore, the method of the '008 patent comprising or consisting of the administration of about 0.1 to 1 mg of calcitonin to insulin-requiring diabetic human species anticipates the instant claims. Given that the method step of the '008 patent and the instant claims is the same, and the amylin agonist calcitonin administered and the amount administered are the same, and the human diabetic patient species to whom calcitonin is administered is the same as the one described in the instant application, the method claimed in the '008 patent is expected to bring about an obesity-treating effect in the intrinsically obese calcitonin-treated diabetic patient species of the '008 patent. Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the teachings of the '008 patent, Beumont's ('008) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the obesity-treating effect. The art-recognized intrinsic obesity being prevalent in 80 to 90% of diabetic patients as disclosed by Tsanev (see English abstract), Beumont's ('008) method of administration of the above-identified therapeutically effective amount (i.e., dosage units of about 0.1 to 1 mg) of the amylin agonist calcitonin to 80 to 90% of intrinsically obese type 2 diabetic human subject species anticipates the instant claims.

(10) Response to Appellants' Arguments

(I) In response to the rejection of claims 23, 24, 27, 29, 31-34, 37-39, 68, 72, 76, 80, 82, 84 and 95-97 made in paragraph 24 of the Office Action mailed 02/11/08 and maintained in paragraph 13 of the Office Action mailed 05/28/08 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the full scope, Appellants submit the following **arguments**.

(a) The proper standard for determining compliance with the enablement requirement is whether the specification provides sufficient information to permit one skilled in the art to make and use the claimed invention. *United States v. Telectronics, Inc.,* 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. A considerable amount of experimentation is permitted, provided that it is merely routine, or provided that the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands,* 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A specification that discloses how to make and use a claimed invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented "must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein." *In re Brana, 51* F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995) (quoting *In re Marzocchi,* 439 F.2d 220, 223,169 U.S.P.Q. 367, 369 (C.C.P.A. 1971).

(b) Regarding the quantity of experimentation needed, the standard for determining enablement is whether the experimentation needed to practice the invention is undue or unreasonable. *Mineral Separation v. Hyde,* 242 U.S. 261,270 (1916). One of ordinary in them would have the ability to select amylin and amylin agonist peptides for use in the claimed methods without undue experimentation in view of the specification. Methods of synthesis of a defined group of compositions useful in the claimed methods are provided or known in the art, as are methods of administration and methods of weight determination.

(c) Regarding the amount of direction or guidance presented, the specification *broadly* discloses that the claimed amylin or amylin agonist compounds are useful in the treatment of obesity in a subject in need thereof. The specification and claims disclose amylin agonist analogues of the invention with great particularity. There is express guidance as to modes of administration, therapeutic

dosages, mechanisms for assessing therapeutic efficacy, as well as a working example to demonstrate the statistically significant ability of an exemplary amylin compound to treat obesity in a human subject in need thereof. In the working example, the human subjects were Type 2 diabetics. The working example illustrated Type 2 diabetic subjects taking insulin does not render the scope of enablement limited to this subject population. Rather, it demonstrates that in a particularly difficult to treat, obese subject population (Type 2 diabetic subjects taking insulin), an exemplary amylin compound is therapeutically effective in the treatment of obesity. Taken together with the teachings of the specification, the working example provides a base-line approach for establishing therapeutic efficacy of exemplary amylin compounds within the context of the presently claimed methods. Utilizing similar study structures, Appellants have in fact established that exemplary amylin compounds are effective in the treatment of obesity in non-diabetic subjects as well (see, e.g., IDS entries AZ1, AZ2, AZ4 and AZ5 of Aronne *et al.* and Smith *et al.*). This evidence confirms the teachings of the specification, and demonstrates that Appellants' working example in fact provides enablement of the efficacy of a *particularly difficult to treat*, chronically obese subject population.

(d) The Office is impermissibly attempting to limit the scope of enablement to the scope of the working examples. Based on the extensive guidance provided in the specification, including the human clinical study results, as well as the high level of skill in the art, the skilled artisan would be able to evaluate efficacy of amylin compounds in accordance with the methods of the inventions to ascertain therapeutically effective amounts of the recited amylin compounds. The Office's characterization of Example 1 only serves to underscore the enablement of the claims in this regard. Example 1 describes a clinical study wherein routine dosages were evaluated in human clinical subjects to ascertain a therapeutically effective dose as well as effective administration regimens. The working examples, in combination with the disclosure of the specification and knowledge of one skilled in the art, amply enable the full scope of the invention as presently claimed.

(e) With respect to reasons for doubting the objective truth of the specification based on Rink's disclosure as relied upon by Appellants' prior admission in their Appeal Brief filed July 2000 in the parent case, when read in context, it is clear that Rink only contemplates amylin-induced appetite suppression in rodents, not in humans. Rink does not describe the treatment of obesity in humans using amylin or an amylin agonist as required by the claims of the present invention.

(f) Regarding the nature of the invention, Appellants agree with the Office's assertion that the nature of the invention is pertinent to the treatment of obesity in a human subject in need of such treatment comprising or consisting of administering an amylin, an amylin agonist, or an amylin agonist analogue composition or compound in an amount effective to inhibit weight gain or induce weight loss in the subject. Specifically, the invention contemplates the treatment of obesity in human subject in need of treatment by the administration of an amylin or amylin agonist. Appellants state that they discovered that amylin or agonists thereof can be used for the treatment of obesity.

(g) The relative skill of one or ordinary skill in the art to which the invention pertains is very high. Regarding the state of the prior art, Appellants agree in part with the Office's characterization of obesity or adiposity as a 'chronic disease' that is highly prevalent in modern society which is strongly associated with multiple conditions including diabetes mellitus, insulin resistance, hypertension, etc. Indeed, it was Appellants' discovery that amylin or amylin agonists could be administered to a human subject in need of treatment for obesity. In this respect, one of ordinary skill in the art would have the ability to select amylin and amylin agonist peptides for use in the claimed methods without undue experimentation. Indeed, amylin compounds recited in the claims are generally recognized as a defined class of compounds, and the specification provides ample direction and guidance to those skilled in the art with regard to the identification of such amylin compounds useful in the context of the claimed methods.

(h) Regarding the predictability or unpredictability of the art, the Office alleges that the state of the art with regard to the use of amylin in obesity is unpredictable and that Baron *et al.* and Ratner *et al.* indicate the impracticability of using amylin as a therapeutic agent. Both Baron *et al.* and Ratner *et al.* actually support enablement of the claimed invention. Whether native human amylin is suitable for use as a commercial drug product is not a proper standard for judging the enablement of the present claims. Given the teachings of the instant specification, one of ordinary in the art would have the ability to select amylin and amylin agonist peptides for use in the claimed methods without undue experimentation. This further confirms that both amylin and amylin agonists are well known compounds that have been widely characterized. Given this, one of ordinary skill in the art would have the requisite skill to practice the invention commensurate in scope with the claims without undue experimentation.

(i) Regarding the breadth of the claims, in rejecting the claims the Office has impermissibly attempted to limit the invention to the scope of the examples. Such a standard is legally incorrect. As set forth in MPEP 3 2164.02, "[f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation." Tables I-VII and Examples 1-3 disclose data relating to the claimed methods and exemplary amylin compounds. Alone, this disclosure is sufficient such that one of ordinary skill in the art at the time the invention was made would have the ability to practice the invention commensurate in scope with the claims. Appellants disagree with the Office's assertion that the only amylin agonist analogue species within the recited broad genus that is being used for inducing weight loss in humans is pramlintide. Appellants allege that the Office appears to be focusing on Examples rather than the teachings of the specification as a whole and the level of ordinary skill in the art. In this regard, it is noted that amylin compounds recited in the claims are generally recognized as a defined class of compounds, and the specification provides ample direction and guidance to those skilled in the art with regard to the identification of such amylin compounds useful in the context of the claimed methods. Furthermore, the specification is replete with examples of amylin agonists, including functional variants, fragments, and derivatives of amylin and amylin agonists. See e.g. Table VIII and specification page 15, line 1 to page 19, line 5. Given at least the discussion in the background concerning amylin agonists, as well as the description of SEQ ID NO: 12-17, one of ordinary skill in the art having read the specification would have the ability to select known amylin agonists without undue experimentation. Moreover, to the extent that any additional experimentation may be required, the performance of routine and well known steps cannot create undue experimentation even if it is laborious. See *In re Wands* (Id.); *In re Angstadt,* 190 USPQ 214 (CCPA 1976). Given the knowledge in the art, and based on the guidance provided in the specification regarding the extensive exemplary embodiments of amylin compounds, receptor binding assays and other assays for determining amylin activity, including the soleus muscle assay, and exemplary clinical study designs, additional therapeutically active amylin agonists can be identified within the context of the present claims without the need for undue experimentation. The specification provides numerous examples of compounds within the scope of the recited genus, and guidance with regard to assays and clinical

studies in the examples useful to evaluate the efficacy of the compounds in the methods of the present invention. Based on such guidance, one of skill in the art would be able to practice the claimed invention with only routine experimentation.

(j) Certain of the dependent claims recite specific types of amylin compounds. As generally understood by those of skill in the art, amylin analogues are compounds that are structurally related to the reference compound, i.e., amylin. As explained in the specification and understood by those having ordinary skill in the art, *an amylin analogue can have one or more amino acid substitutions, deletions, inversions, or additions compared to a native or naturally occurring amylin*. Furthermore, the claims 2 clarify that the amylin analogue is an amylin agonist analogue. In accordance with the claims and the knowledge of those of ordinary skill in the art, the recited amylin agonist analogues are both structurally and functionally defined. With regard to the Office's position on the scope of various claim terms and transitional phrases, various claim terms such as obesity and administering are discussed in a broad context. While Appellants do not necessarily agree with the exact definition provided by the Office, Appellants do acknowledge the broad scope of such terms commensurate with the present specification. With regard to the use of traditional transitional phrases such as 'comprising', 'consisting of' and 'consisting essentially of', such language has been used in the traditional context. Within the context of the claimed methods for treating obesity, such terms of art would have their traditional meanings and limitations with regard to claim elements relevant to the treatment of obesity. However, such traditional claim terms would have no bearing on components, steps, or elements outside of the claimed scope of the treatment of obesity.

(k) With regard to Office's noting of Appellants' previous acknowledgment that administration of amylin would have lead to *weight gain* rather than *weight decrease* as was known at the time of the invention via the disclosure of US patents 5,364,841 and 5,280,014, and Appellants' previous express statement (see pages 7 and 8 of Appellants' amendment filed 03/22/99 in the parent application 08/870,762) that at the time of the invention, amylin was administered to patients suffering from *anorexia* or *a similar condition* 'in order to increase weight', Appellants state the following: (a) The subject matter of '367 Rink is not germane to the current claims; (b) Anorectic subjects are not in need of treatment for obesity.

(l) The amylin agonist analogue of claim 68, 72, 76, 84 and 97 comprise a defined amino acid sequence support for which may be found at page 15 of the specification. Amylin agonists of these claims are well known compounds that have been widely characterized, 'including use in treatment of obesity'. However, Appellants fail to substantiate this via citation of any publications or evidence.

The Office submits the following **response** to Appellants' arguments:

In the instant application, except for one amylin agonist species, pramlintide, Appellants have not established that a representative number of the vast number of exemplary amylin compounds encompassed within the scope of the claims is indeed effective in the treatment of obesity in diabetic or non-diabetic subjects in need of treatment for obesity. With regard to the use of amylin and non-pramlintide or non-calcitonin amylin agonists in the treatment of obesity in humans, the Office agrees with Appellants that *the prior art does not disclose the subject matter of the claims of the present application*. It is because of this reason, one of skill in the art would look into Appellants' specification for specific guidance and direction to practice the full breadth of the instantly claimed method, but which is lacking. A mere description of methods of synthesizing amylin agonist peptides is not sufficient to enable the full scope of the method of treating obesity as claimed. Even if a skilled artisan selected some of the exemplary amylin agonist analogues recited in the instant specification, there is no predictability that said non-pramlintide amylin agonist analogues would have the therapeutic effect against a particularly difficult to treat obese diabetic or morbidly obese human subjects and is usable in the claimed method, with or without concurrent insulin treatment.

With regard to Appellants' statement that an amylin analogue can have one or more amino acid substitutions, deletions, inversions, or additions compared to a native or naturally occurring amylin, it should be noted that, other than pramlintide, no amylin analogues having one or more amino acid substitutions, deletions, inversions, or additions compared to a native or naturally occurring amylin have been shown to be effective in treating obesity and therefore usable in the methods as claimed. How to make one or more than one substitutions, deletions, inversions, or additions in an amylin analogue in such a way that the resultant products would still have obesity-inducing effect or weight loss-inducing effect is neither taught by Appellants, nor is it known in the state of the art.

With regard to the quantity of experimentation needed, the standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: 'is the experimentation needed to practice the invention undue or unreasonable'. That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In the instant case, no guidance or direction has been provided in the instant specification so that one could predict which of the amylin agonist analogue species other than pramlintide would have the requisite therapeutic effect against obesity. Because there is no way to predict *a priori* which amylin, amylin agonists, or amylin agonist analogues from the specification or from the chemical structures alone would be therapeutically active against obesity in diabetic or non-diabetic humans subjects, including morbidly obese human subjects, an extraordinary amount of trial and error experimentation is required to identify the obesity-treating amylin agonist analogue species. Assuming *arguendo* that the experimentation required is routine, if one of skill in the art screens innumerable non-pramlintide amylin agonist species or amylin agonist analogue species currently encompassed within the recited genus, including those disclosed in Examples 2 and 3 or Table II on page 32 of the instant application, using receptor binding assays, and assays for amylin activity, there is absolutely no predictability that a non-pramlintide amylin agonist having amylin activity would have an obesity-relieving effect, weight loss-inducing effect, or food intake-reducing effect given the Applicants' admission that amylin itself has no effect on food intake. Given this and the lack of showing within the instant specification as explained above, the weight loss-inducing or obesity-relieving effect of any amylin or any non-pramlintide amylin agonist analogue mimicking effect(s) of amylin, administered alone or as an adjunct to insulin therapy, to an obese diabetic or obese non-diabetic human subject, is simply not predictable. Applicants have provided no guidance with regard to the use of extraordinarily large genus of amylins, amylin agonists, and amylin agonist analogues in the treatment of obesity in humans. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states: 'The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art'. The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or *how to use* the invention. The more is known in the prior art about the nature of the invention, how to make, *and* how

to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling' (MPEP 2164.03). MPEP also states that physiological activity can be considered inherently unpredictable. Whether the specification would have been enabling *as of the filing date* involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art. The state of the prior art is what one skilled in the art would have known, *at the time the application was filed*, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains *at the time the application was filed*. See MPEP § 2164.05(b). None of the post-filing references and abstracts cited by Appellants represents the state of the art *at the time of filing*. The abstracts of Aronne *et al.* (*Obesity* 14: A17, 2006) and Smith *et al.* (*Diabetes* 56: A88, 2007) submitted by Appellants are silent about the diabetic or non-diabetic status of the subjects included in the study. Both are limited to the use of the single amylin agonist analogue species, pramlintide, in the method described therein. The post-filing teachings of Aronne *et al.* (*J. Endocrinol. Metabol.* 92: 2977-2983, 2007) and Smith *et al.* (*J. Am. J. Physiol. Endocrinol. Metabol.* 293: 620-627, 2007) submitted by Appellants are also limited to the use of one amylin agonist analogue species, pramlintide, for reducing caloric intake and meal size, or for reducing body weight. These two post-filing publications support the Office's position on the lack of enablement of the full scope of the instant claims by confirming that *even about a decade after the effective filing date of the instant application*, the only amylin agonist analogue species within the recited broad genus that is being used for inducing weight loss in humans is pramlintide.

With regard to Appellants' arguments on the reasons for doubting the objective truth of the specification particularly in connection with amylin, a nonpramlintide amylin agonist, or a non-pramlintide amylin agonist analogue, the following should be noted. A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented

must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, *unless* there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). In the instant case, one of the reasons for doubting the objective truth of the statements comes from Appellants' own statement. For example, Appellants have readily acknowledged previously that administration of amylin would have lead to *weight gain* rather than *weight decrease* as was known at the time of the invention via the disclosure of US patents 5,364,841 and 5,280,014. Appellants have expressly stated previously that *at the time of the invention*, amylin was administered to patients suffering from *anorexia* or *a similar condition* 'in order to increase weight'. See pages 7 and 8 of Appellants' amendment filed 03/22/99. Thus, *at the time of the invention*, amylin at a dose varying from about 0.1 to 10 mg (which dose encompasses the doses recited in the instant claims, including claims 23, 33, 80, 82 and 84) was administered to treat patients suffering from *anorexia* or *patients deficient in adipose tissue*. See also claims and page 13 of Rink *et al.* (WO 9220367). Note that the instantly recited 30 to 300 micrograms per dose of amylin falls within Rink's anorexia-treating dose. This alone is *prima facie* evidence for the lack of scope of enablement of the instantly claimed method of treating obesity as claimed comprising administration of amylin as claimed. Therefore, despite the level of skill in the art and despite the structural relatedness to pramlintide, there is no predictability that administration of a dose of amylin varying from about 0.1 to 10 mg to a human patient in need of treatment for obesity would have resulted in inhibition of weight gain or induction of weight loss. Instead, one of skill in the art would have expected induction of weight gain upon administration of amylin as acknowledged by Appellants. With the weight gain-increasing effect of amylin known at the time of the invention, one of skill in the art would have reasonably expected amylin and the innumerable number of non-pramlintide amylin agonists or amylin agonist analogues encompassed within the scope of the instant claims, to be therapeutic for anorexia. The administration of amylin or a non-pramlintide amylin agonist analogue would *not* have predictably brought about weight gain-inhibiting or weight loss-inducing effect. Thus, in view of level of skill, the state of the art at the time of the invention, and the information in the specification, one of skill would *not* expect that the recited genus could be used in that manner without undue experimentation. Therefore, the

considerable amount of experimentation needed in the instant case is not merely routine, but undue in view of the unpredictability and the lack of evidence enabling the full scope of the invention.

The post-filing references of Aronne et *al.* and Smith et *al.* cited by Appellants do not show that administration of any amylin or any non-pramlintide amylin agonist analogue as claimed in the instant claims results in obesity relief or induction of weight loss in diabetic or non-diabetic human subjects in need of treatment for obesity. Furthermore, Appellants themselves have established the direct relevance of Rink's ('106) disclosure to humans via their following statements. Appellants have previously gone on the record with the following (see pages 9, 13 and 14 of Appellants' Appeal Brief filed 24 July 2000 in the parent application 08/870,762) [Emphasis in original]:

> .... THE RINK PATENT PROVIDES THAT AMYLIN AND AMYLIN AGONISTS ADMINISTERED AS DESCRIBED AND CLAIMED IN THE PRESENT APPLICATION HAVE "NO MEASURABLE EFFECT" ON FOOD INTAKE.
>
> .... the Rink patent reports that a 1.0 μg/kg dose (**equivalent to about 70μg/dose in an adult human**) had no effect on food intake. [Emphasis in bold added]

Therefore, there was no predictability that administration of a dose varying from about 0.1 to 10 mg of amylin to a human patient would have resulted in inhibition of weight gain or induction of weight loss. Instead of weight loss, one of skill in the art would have expected induction of weight gain. This is yet another reason for doubting the objective truth of the specification. Furthermore, with the art-reported instability of amylin in solution and its tendency to aggregate, one of skill in the art would not have been able to determine an amount effective to reduce weight loss or relieve obesity without undue experimentation. In view of this, Appellants' description of exemplary amylin agonist compounds alone is insufficient to enable the full scope of the claimed invention. Because of the admitted therapeutic efficacy of amylin against anorexia, one of skill in the art could not have predictably selected non-pramlintide amylin agonist species or non-pramlintide amylin agonist analogue species for treating obesity without considerable amount of undue experimentation. Thus, in view of level of skill, the state of the art at the time of the invention, and the information in the specification, one of skill would *not* expect that the recited genus could be used in that manner without undue experimentation.

In sum, contrary to Appellants' allegation, a *prima facie* case of lack of scope of enablement has been established by providing sufficient references and specific technical reasons along with the

documentation of Appellants' own previous statements. Given the knowledge in the art of the therapeutic effect of amylin against anorexia despite its amylin agonistic characteristics as measured by receptor binding assays and the soleus muscle assay etc., the breadth of the claims, the lack of predictability when viewed in combination with Rink's ('367) showing that the administration of about 0.1 to 10 mg amylin is therapeutic against anorexia, Appellants' own previous acknowledgment that administration of amylin would have lead to *weight gain* rather than *weight decrease* as was known at the time of the invention, Appellants' own previous acknowledgment that amylin and amylin agonists have no measurable effect on food intake, the lack of working examples enabling the full scope of the claimed invention, a considerable amount of non-routine undue experimentation would have been required to reproducibly practice the full scope of the invention, as claimed. Instant claims do not meet the scope of enablement provisions of 35 U.S.C. § 112, first paragraph.

For the reasons delineated above, the scope of enablement rejection should be sustained.

(II) In response to the rejection of claims 33 and the dependent claims 34, 37-39, 72, 82 and 96 made in paragraph 23 of the Office Action mailed 02/11/08 under 35 U.S.C § 112, first paragraph, as containing new matter, Appellants submit the following **arguments**.

With regard to the Office's lack of descriptive support for the transitional term of art 'consisting of administering' in claim 33, Appellants argue that the term 'consisting' used in claim 33 is a term of art that need not be specifically recited in the specification. Appellants state that ample support for the phrase 'method of treating obesity .... consisting of administering' is found throughout the specification, e.g. abstract and lines 9-12 of page 2 (i.e., a therapeutically effective amount of an amylin or amylin agonist alone or in conjunction with another obesity relief agent).

The Office's **rebuttal** is provided herein below.

It should be noted that the recitation of an obesity relief agent consisting of an amylin or amylin agonist alone cannot provide support for the method step of 'consisting of administering' a composition as recited in claim 33. A method of treatment of obesity 'consisting of' such an administration step *excludes,* for example, simultaneous insulin administration, or insulin administration minutes or hours before or after the administration. However, neither the original claims, nor the abstract or lines 9-12 of page 2 of the specification support such a method of

treating obesity 'consisting of' administering the recited composition. The originally filed specification at lines 10-13 of page 12 of the specification states [Emphasis added]:

> The present invention is directed to novel methods for treating or preventing obesity in humans *comprising* the administration of an amylin or an amylin agonist, the amylin agonist analogue ^{25,28,29}Pro-human amylin.

Pages 28-29 and Table I describe a statistically significant reduction in the mean baseline weight seen after the subcutaneous administration of 60 micrograms TID or 60 micrograms QID of one specific amylin agonist analogue species, pramlintide, to type II diabetic subjects for four weeks, wherein said pramlintide administration was accompanied *with the continued administration of insulin*. The method of treatment of obesity as described in the originally filed specification comprised insulin treatment *and* the administration of a specific dose of pramlintide to type II diabetic patients. This however does not provide descriptive support for the now claimed method of treating obesity in a human in need of treatment for obesity, said method 'consisting' of administering to said subject an amount of a composition as recited.

For the reasons delineated above, the new matter rejection should be sustained.

(III) In response to the rejection of claims 23, 24, 27, 29, 31, 33, 34, 37-39, 80 and 82 made in paragraph 26 of the Office Action mailed 02/11/08 and maintained in paragraph 14 of the Office Action mailed 05/28/08 under 35 U.S.C § 102(b) as being anticipated by Kolterman *et al*. ('220) as evidenced by Tsanev, Appellants submit the following **arguments**.

(a) Appellants cite case law and MPEP §2131 and assert that in order to anticipate a claim, a single prior art reference must provide each and every element set forth in the claim, and that the identical invention must be shown in complete detail as it is contained in the claim.

(b) Kolterman '220 describes the use of an amylin agonist (i.e., pramlintide) for treating type II diabetes mellitus. Kolterman '220 merely demonstrates that administration of an amylin agonist significantly reduces postprandial plasma glucose concentrations in patients with type II diabetes mellitus. Kolterman '220 does not teach the use of an amylin or an amylin agonist for treating obesity or demonstrate a reduction in body weight in those patients administered an amylin or an amylin agonist. Kolterman '220 is silent with regard to the effect of an amylin or an amylin agonist on body weight.

(c) Kolterman '220 at page 7, first paragraph, discloses that the hyperglycemia associated with Type II diabetes can sometimes be reserved or ameliorated by diet or weight loss. With respect to the use of amylin or amylin agonists for treatment of obesity in a subject in need thereof, Kolterman '220 is silent. Whether or not Kolterman '220 discloses that weight loss is beneficial is irrelevant, at least because the Office has failed to state a nexus between administration of an amylin or agonist thereof and treatment for obesity.

(d) In an attempt to cure the deficiency in Kolterman '220, the Office relies on Tsanev to allegedly provide evidence that 80-90% of diabetic patients are obese. However, the 80-90% of obese diabetic patients alleged by Tsanev falls short of the 100% (i.e., always, under any circumstances) criterion required by the claims and required by the law. Thus, Kolterman '220 as evidenced by Tsanev does not provide each and every element of the claimed invention, at least because Kolterman '220 (with or without Tsanev) is silent with respect to treatment of obesity with amylin or agonists thereof, or the intended population for treatment (i.e., human subject in need of treatment for obesity) of the current claims.

The Office submits the following **response** to Appellants' arguments:

Contrary to Appellants' assertion, the prior art method necessarily includes *all* of the elements of the instant claims. Clearly, the Office has set forth a *prima facie* case of anticipation. As set forth previously, Kolterman *et al.* ('220) taught a method of administering to an insulin-taking type II diabetic human subject a dose of 10, 30, 50, 60 or 150 micrograms per day (i.e., the amount falling in the range recited in the instant claims) of the amylin agonist composition, pramlintide or $^{25, 28, 29}$pro-h-amylin, also known as AC137, i.e., the same amylin agonist administered in Example 1 of the instantly invention. The composition consisted of pramlintide and a pharmaceutically acceptable carrier, and was administered in single or multiple doses, for example, of about 30 micrograms QID, or about 60 micrograms TID or QID, i.e., an amount effective to treat obesity. See pages 9-11; paragraph bridging pages 20 and 21; page 21; first paragraph on page 19; lines 8-10 on page 19; and the first row reciting 'Insulin-Treated Patients' in each Table of Kolterman *et al.* ('220). Pramlintide was administered subcutaneously 1-4 times a day, before meals. See pages 9 and 22. Kolterman *et al.* ('220) additionally taught that the presence of obesity is a characteristic of 'most patients with Type II diabetes mellitus'. See page 10. Kolterman *et al.* ('220) taught the benefit of obtaining weight loss in

Type II diabetic patients by teaching that hyperglycemia associated with Type II diabetes can be reversed or ameliorated by *weight loss* sufficient to restore the sensitivity of the peripheral tissues to insulin (see pages 7, first paragraph), thus teaching that Type II diabetic patients are indeed in need of treatment for obesity or weight loss. Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the teachings of Kolterman *et al*. ('220), Kolterman's ('220) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the obesity-treating effect in the type II diabetic patient species. The Office's position that Kolterman's ('220) method is the same as the Appellants' claimed method is based upon the fact that the method step, the pramlintide compound administered, the amount of the compound administered, the route by which the compound is administered, and the intrinsically obese type II diabetic human patient species to which the pramlintide compound is administered, are the *same* in the two methods. The art-recognized intrinsic obesity being prevalent in 80 to 90% of diabetic patients as disclosed by Tsanev (see abstract), Kolterman's ('220) method of administration of the above-identified therapeutically effective amount (i.e., about 30 micrograms QID, or about 60 micrograms TID or QID, or a dose of 10, 30, 50, 60 or 150 micrograms per day) of the amylin agonist ^{25,28,29}Pro-human amylin to intrinsically obese type 2 diabetic human subject species anticipates the instant claims. Given Tsanev's express disclosure that 80 to 90% of type II diabetic patients are intrinsically obese, and given Kolterman's ('220) recognition that obesity is an intrinsic characteristic of most patients with Type II diabetes mellitus and the indication that these patients are in need of weight loss, Kolterman's ('220) method of subcutaneous administration of pramlintide to Type II diabetic patients in an amount that falls within the range recited in the instant claims, necessarily serves as the claimed method of treating obesity, and therefore anticipates the instantly claimed method. That 10-20% of Kolterman's ('220) diabetic patients, also to whom pramlintide is administered, are not expected to be obese is not relevant since an anticipatory reference does not have teach every species or every embodiment encompassed by the scope of the claims. Given that the method step of the Kolterman's ('220) method and the instant claims are the same, Kolterman's ('220) method is expected to bring about the obesity-treating effects, weight gain-inhibiting effects, or weight loss-causing therapeutic effects in the intrinsically obese pramlintide-treated type II diabetic patient species. Contrary to Appellants' assertion, the prior art method necessarily includes *all* of the elements of the instant claims.

That the determination of inherency in the instant case is certainly not established by probabilities or possibilities is further evidenced by the teachings of Thompson *et al.* (May 1997). Thompson *et al.* (May, 1997) showed that a method of subcutaneous administration of pramlintide, i.e., $^{25, 28, 29}$pro-h-amylin, an analog of human amylin, i.e., an amylin agonist, to patients with type II diabetes requiring insulin, at a dose 60 micrograms QID (i.e., four times a day) or TID (i.e., three times a day) not only improved glycemic control in these patients, but ***also decreased body weight concurrently*** (see abstract). Therefore, Kolterman's ('220) method necessarily served as a method of treating obesity. Since the prior art clearly taught the instantly claimed method, any assertions of specific functional properties attributed to the amylin agonist pramlintide administered in the claimed method are merely inherent and do not necessarily make the claimed method patentable. *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.). In the instant application, the obesity-relief, weight gain inhibition, or weight loss-induction is an inherent property inseparable from the administered pramlintide. The two structurally identical pramlintide compounds administered in the two methods (i.e., the prior art method and the instant method) cannot have mutually exclusive properties. The same two methods cannot have mutually exclusive results.

To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed.

Cir. 1999). See MPEP 2124. The alleged failure of Kolterman ('220) to expressly mention treatment of obesity as a goal is irrelevant. To the extent the method embodiment in the claimed invention achieves treatment of obesity, so does the method of Kolterman's ('220). Where the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results. See *Mehl/Biophile International Corp. v. Milgraum*, U.S. Court of Appeals Federal Court, 52 USPQ2d 1303 and 1306, 192 F3d 1362, 1999 citing *W.L. Gore & Assocs. v. Garlack, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983).

It is a commonly known fact in the art that type II diabetic patients (80-90% of whom are known to be obese) are 'in need of' obesity. Appellants themselves characterize Type 2 diabetic subjects taking insulin as a particularly difficult to treat ***obese*** subject population. See first full paragraph of page 25 of Appellants' after-final amendment filed 05/12/08 and top of page 16 of Appellants' appeal brief filed July 2000 in the parent application 08/870,862. With regard to Appellants' statement that Tsanev's disclosure that 80-90% of diabetic patients are obese falls short of the 100% (i.e., always, under any circumstances), the following must be noted. 'A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus'. The species in that case will anticipate the genus. *In re Slayter*, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); *In re Gosteli*, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989). A genus does not always anticipate a claim to a species within the genus. However, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. In *In re Sivaramakrishnan*, 673 F.2d 1383, 213 USPQ 441 (CCPA 1982), the claims were directed to polycarbonate containing cadmium laurate as an additive. The court upheld the Board's finding that a reference specifically naming cadmium laurate as an additive amongst a list of many suitable salts in polycarbonate resin anticipated the claims. The applicant had argued that cadmium laurate was only disclosed as representative of the salts and was expected to have the same properties as the other salts listed while, as shown in the application, *cadmium laurate had unexpected properties*. The court held that it *did not matter that the salt was not disclosed as being preferred, the reference still anticipated the claims* and because the claim was anticipated, *the unexpected properties were immaterial*. Although the instant claims are method claims, in the instant application, the prior art disclosure of a method comprising or consisting of the administration of 30 or micrograms of the amylin agonist,

^{25,28,29}Pro-human amylin, to 80-90% of the human diabetic patients anticipates the instantly claimed method. The claims are anticipated because the administered ^{25,28,29}Pro-human amylin also inherently exerted obesity-relieving effects in said method. See also *Ex parte Novitski*, cited *supra*.

In the instant application, it is important to note that the *human patient species used in Example 1 of the instant specification for treatment of obesity via administration of pramlintide are indeed type II diabetic human patient species*. Thus, the prior art disclosure is commensurate in scope with the instant disclosure with regard to the type 2 diabetic human subject population used, the pramlintide compound administered, the amount and the frequency of pramlintide administered to the type 2 diabetic human patient species. In the instant case, the claims are drawn to a method of treatment of obesity that uses generic human subjects. The method is not limited to treating obesity in non-diabetic obese human patients, but encompasses treating obesity in type II diabetic human patients, 80-90% of whom are known in the art to have intrinsic obesity. In other words, treatment of obesity in type II diabetic human patients is just one of the species or embodiments encompassed within the scope of the genus of human subjects in need of such treatment. That 10-20% of the prior art diabetic patients, to whom pramlintide is administered, are not expected to be obese is not relevant, since an anticipatory reference has to teach only one species or one embodiment encompassed by the scope of the genus claims. Under the principles of inherency, a reference may be directed to an entirely different problem than the one addressed by the inventor, or may be from an entirely different field of endeavor than that of the claimed invention, yet the reference is still anticipatory if it explicitly or inherently discloses every limitation recited in the claims. See *State Contracting & Eng'g Corp. v. Condotte America, Inc.*, 346 F.3d 1057, 1068, 68 USPQ2d 1481, 1488 (Fed. Cir. 2003). Appellants appear to be arguing that in order to be anticipatory, a prior art reference has to teach each and every species or embodiment encompassed within the scope of the claims. The argument is not persuasive.

For the reasons delineated above, the art rejection should be sustained.

(IV) In response to the rejection of claims 23, 24, 27, 29, 31, 33, 34, 37-39, 80 and 82 made in paragraph 28 of the Office Action mailed 02/11/08 and maintained in paragraph 16 of the Office Action mailed 05/18/08 under 35 U.S.C § 102(b) over Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996) (Kolterman *et al.*, 1996) as evidenced by Itasaka *et al.* (*Psychiatr. Clin. Neurosci.* 54: 340-341, June 2000), Appellants submit the following **arguments**.

(a) Kolterman 1996 merely describes the use of an amylin agonist, pramlintide, for treating patients with insulin-dependent diabetes mellitus and demonstrates *inter alia* that administration of the amylin agonist significantly reduces postprandial plasma glucose concentrations. Kolterman 1996 discloses neither the use of the amylin agonist for treating obesity nor a reduction in body weight in those patients administered the amylin agonist. Kolterman 1996 does not report the weight of the subjects at the end of the study and nothing in the reference indicates that pramlintide had any effect on the weight of the subjects. Kolterman 1996 is silent with regard to the effect of the amylin agonist on body weight. In an effort to cure the deficiencies of Kolterman 1996, the Examiner relies on Itasaka to allegedly provide a correlation between body mass index (BMI) and obesity. However, nothing in Kolterman 1996 (with or without evidence of Itasaka) suggests that an amylin agonist can be useful in the treatment of obesity, or in the selection of a subject population for such method of treatment. The patient population of Kolterman 1996 is not necessarily the same as the claimed subject, *i.e.,* a subject in need of treatment for obesity.

(b) The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert, 9* F.3d 1531, 1534 (Fed. Cir. 1993). "To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the references, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson* 169 F.3d 743,745 (Fed. Cir. 1999).

The Office submits the following **response** to Appellants' arguments:

Contrary to Appellants' assertion, the prior art method necessarily includes *all* of the elements of the instant claims. Clearly, the Office has set forth a *prima facie* case of anticipation.

As set forth previously, Kolterman *et al.* (1996) taught a method of subcutaneous administration of 30, 100, or 300 μg of pramlintide composition or AC137 (i.e., $^{25, 28, 29}$pro-h-amylin, the one used in Appellants' Example 2), a human amylin analogue, to human patients with insulin-dependent diabetes mellitus or IDDM who are on insulin. Pramlintide was administered three times daily for a period of 14 days. See abstract; and page 493. The mean body weight $\pm$ SEM of diabetic patients included in Kolterman's (1996) method who were administered subcutaneously with 30 micrograms, 100

micrograms, and 300 micrograms of pramlintide, three times a day for 14 days, was 70.6 $\pm$ 2.7, 74.4 $\pm$ 2.5, and 75.7 $\pm$ 2.6 respectively, a body weight similar to the 70 kg body weight of the human patient species disclosed in the last paragraph of page 27 of the specification. Note that the human patient in need of the recited treatment according to the instant invention is expressly identified in the instant specification as one having a body weight of 79 kg. The recited therapeutic amount range of 'about 0.1 milligrams per day to about 1 milligram per day', or 'about 0.01 to about 5 mg/day', or 0.03 to about 5 mg/day of the amylin agonist or amylin agonist analogue, pramlintide, administered is specifically "for a 70 kg patient". See last paragraph of page 27 of Applicants' specification. Therefore, the 70.6 to 75.7 kg diabetic patients from Kolterman's (1996) study qualify as 'human subjects in need thereof' as recited in the instant claims. Additionally, even body mass index (BMI)-wise, Kolterman's (1996) diabetic subjects meet the limitation 'human subjects in need of treatment of obesity' as recited in the instant claims, because the diabetic subjects included in Kolterman's method (1996) had a BMI of up to 27. See second full paragraph under 'Subjects, materials and methods'. Therefore, Kolterman's (1996) diabetic subjects having a BMI at least in the range of 24 up to 27 do qualify as obese diabetic subjects in light of what is known in the art. For example, Itasaka *et al.* teach that a BMI of 24.0 to 26.4 represents mild obesity and 26.4 and heavier (i.e., including a BMI of 26.4 to 27) represents obesity in humans (see abstract of Itasaka *et al.*). Note that Kolterman's (1996) pramlintide composition did not comprise another obesity relief agent, but consisted of pramlintide. The pramlintide composition was injected subcutaneously to the diabetic human patients (see the section 'Study design') and therefore is expected to inherently contain a pharmaceutically acceptable carrier therein. The amount administered was 30 or 100 micrograms three times a day or 300 micrograms per day. See the section 'Study design'; Table 1; and paragraph therebelow. Clearly, Kolterman's (1996) subcutaneous administration of a therapeutically effective amount of the amylin agonist ^{25,28,29}Pro-human amylin to diabetic human subjects weighing 70 kg or more, or having a BMI falling in the BMI range of 24 up to 27 anticipates the instant claims. Thus, the very active step recited in the instantly claimed method was disclosed and practiced by Kolterman *et al.* in April, 1996. The prior art method of administering the above-explained amount of the amylin agonist ^{25,28,29}Pro-human amylin (pramlintide) to diabetic human subjects weighing 70 kg or more, and/or having a BMI falling in the range of 24 up to 27, a BMI similar to the BMI of Appellant's diabetic subjects (see lines 25 and

26 of page 35 of the instant specification) necessarily serves as the Appellants' method. Given that the method step in Kolterman's (1996) method and the instant claims are the *same* and the amount of pramlintide administered are the *same*, Kolterman's (1996) method is expected to necessarily bring about the same therapeutic effect in the pramlintide-treated diabetic patients as defined in the instant invention, i.e., by controlling body weight for cosmetic purposes, or by improving bodily appearance in the diabetic patients, or by inhibiting weight gain. That the determination of inherency in the instant case is certainly not established by probabilities or possibilities is further evidenced by the teachings of Ratner *et al.* (*Exp. Clin. Endocrinol. Diabetes* 113: 199-204, 2005) (Ratner *et al.*, 2005). The reference of Ratner *et al.* (2005) is set forth herein solely to address Appellants' arguments. The reference of Ratner *et al.* (2005), which is co-authored by the inventor OG Kolterman, shows that subcutaneous administration of 30 or 60 micrograms of TID or QID pramlintide to insulin-taking IDDM patients having a body weight of 76.0 $\pm$ 14.3 kg or a BMI of >25 kg/m^2, **concurrently induced *a significant decline in weight***. See sections 'Subjects and Methods'; Results; Table 1; and Figure 1B of Ratner *et al.* (2005). Therefore, this is *prima facie* evidence that Kolterman's (1996) method necessarily served as a method of treating obesity. It is particularly noted that Appellants have advanced no arguments with regard to the teachings of Ratner *et al.* (2005), the reference that was cited to show that the missing inherent matter is necessarily present in the method thing described in the prior art reference of Kolterman *et al.* (1996).

In sum, since the prior art clearly taught the instantly claimed method, any assertions of specific functional properties attributed to the amylin agonist pramlintide administered in the claimed method are merely inherent and do not necessarily make the claimed method patentable. *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.). In the instant application, the obesity-relief, weigh gain inhibition, or weight loss-induction is an inherent property inseparable from the administered pramlintide. Since the

structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the disclosure of Kolterman *et al.* ('1996), Kolterman's ('1996) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the obesity-treating effect or weight loss-inducing effect. The two structurally identical pramlintide compounds administered in the two methods (i.e., the prior art method and the instant method) cannot have mutually exclusive properties. The same two methods cannot have mutually exclusive results. As set forth above, this is evidenced by the teachings of Ratner *et al.* (2005), which is co-authored by the inventor OG Kolterman.

'To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). See MPEP 2124. Itasaka's extrinsic evidence makes clear that the missing descriptive matter, i.e., a BMI of 24.0 to 26.4 as present in Kolterman's diabetic patients represents mild obesity and a BMI of 26.4 and heavier as present in Kolterman's diabetic patients (i.e., including a BMI of 26.4 to 27) represents obesity in humans, and therefore is necessarily present in the method thing described by Kolterman *et al.* (1996). The method of Kolterman *et al.* (1996) clearly anticipates the claimed method of the instant invention, because Kolterman *et al.* (1996) taught the very step of the instantly claimed method in human IDDM patients. The alleged failure of Kolterman *et al.* (1996) to expressly mention treatment of obesity as a goal is irrelevant. To the extent the method embodiment in the claimed invention achieves treatment of obesity, so does the method of Kolterman *et al.* (1996). Where the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results. See *Mehl/Biophile International Corp. v. Milgraum*, U.S. Court of Appeals Federal Court, 52 USPQ2d 1303 and 1306, 192 F3d 1362, 1999

citing *W.L. Gore & Assocs. v. Garlack, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983).

'A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus'. The species in that case will anticipate the genus. *In re Slayter*, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); *In re Gosteli*, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989). A genus does not always anticipate a claim to a species within the genus. However, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. In *In re Sivaramakrishnan*, 673 F.2d 1383, 213 USPQ 441 (CCPA 1982), the claims were directed to polycarbonate containing cadmium laurate as an additive. The court upheld the Board's finding that a reference specifically naming cadmium laurate as an additive amongst a list of many suitable salts in polycarbonate resin anticipated the claims. The applicant had argued that cadmium laurate was only disclosed as representative of the salts and was expected to have the same properties as the other salts listed while, as shown in the application, *cadmium laurate had unexpected properties*. The court held that it *did not matter that the salt was not disclosed as being preferred, the reference still anticipated the claims* and because the claim was anticipated, *the unexpected properties were immaterial*. Although the instant claims are method claims, in the instant application, the prior art disclosure of a method comprising or consisting of the subcutaneous administration of 30 micrograms, 100 micrograms, and 300 micrograms of pramlintide, three times a day for 14 days of the amylin agonist, ^{25,28,29}Pro-human amylin, to the human diabetic patient species weighing 70 kg or more, and/or having a BMI falling in the range of 24 up to 27 anticipates the instantly claimed method which uses generic human subjects in need of treatment of obesity. The claims are anticipated because the administered ^{25,28,29}Pro-human amylin also inherently exerted obesity-relieving effects in said method. See also *Ex parte Novitski*, cited *supra*.

In the instant case, the claims are drawn to a method that uses generic human subjects in need of treatment of obesity. The generic limitation 'human subject' in the instant claims does not exclude 'a 70 kg patient'. The method is not limited to treating obesity in non-diabetic obese human patients, but encompasses treating obesity in type I diabetic human patients weighing 70 kg or more, and/or having a BMI falling in the range of 24 up to 27. In other words, treatment of obesity in type I diabetic human patients is just one of the species or embodiments encompassed within the scope of the genus of human subjects in need of such treatment. An anticipatory reference has to teach only one species or one

embodiment encompassed by the scope of the genus claims. Furthermore, under the principles of inherency, a reference may be directed to an entirely different problem than the one addressed by the inventor, or may be from an entirely different field of endeavor than that of the claimed invention, yet the reference is still anticipatory if it explicitly or inherently discloses every limitation recited in the claims. See *State Contracting & Eng'g Corp. v. Condotte America, Inc.*, 346 F.3d 1057, 1068, 68 USPQ2d 1481, 1488 (Fed. Cir. 2003). Appellants appear to be arguing that in order to be anticipatory, a prior art reference has to teach each and every species or embodiment encompassed within the scope of the claims. The argument is not persuasive.

For the reasons delineated above, the art rejection should be sustained.

(V) In response to the rejection of claims 23, 24, 29, 33, 34 and 38 made in paragraph 27 of the Office Action mailed 02/11/08 and maintained in paragraph 15 of the Office Action mailed 04/30/08 under 35 U.S.C § 102(e)(2) over Gaeta *et al.* ('411) as evidenced by Tsanev, Appellants reiterate the same arguments that they have presented on the obviousness double patenting rejection over US patent 5,686,411. See the paragraph immediately below for Appellants' arguments on both the rejections and the Office's response.

(VI) In response to the rejection of claims 23, 24, 33 and 34 made in paragraph 21 of the Office Action mailed 02/11/08 and maintained in paragraph 11 of the Office Action mailed 05/28/08 under the judicially created doctrine of obviousness-type double patenting over claims 34 and 35 of Gaeta *et al.* ('411) as evidenced by Tsanev, Appellants submit the following **arguments**.

(a) The alleged prior art does not include all of the elements of the instant claims as required by the law. The references provide no guidance concerning the identification of or intent to treat a subject in need of treatment for obesity. The predecessor court to the Federal Circuit held that the inherency of an advantage and its obviousness are entirely different questions, that which may be inherent is not necessarily known, and that obviousness cannot be predicated on what is unknown. The Office's reliance on inherency in the context of anticipation in the obviousness-type double patenting rejection is contrary to the law. *In re Shetty*, 566 F.2d 81, 86, 195 USPQ 753, 756-757 (CCPA 1977).

(b) Claims 23, 24, 33 and 34 are directed to the treatment of obesity in a human in need of treatment thereof. Claims 34 and 35 of Gaeta are merely directed to methods for the treatment of diabetes mellitus in a mammal comprising the administration of a therapeutically effective amount of a particular amylin agonist analogue. Gaeta makes no disclosure that amylin or agonist thereof is effective in the treatment of obesity.

(c) In an attempt to cure the deficiency of claims 34 and 35 of Gaeta, the Office relies on Tsanev to assert that 80-90% of diabetic patients are obese. Even in view of Tsanev, a claim to treating diabetes mellitus with an amylin agonist analogue (i.e., claims of Gaeta) does not teach or suggest treating subjects as currently claimed. Nothing in the cited claims teaches or suggests the identification of or intent to treat a subject in need of treatment for obesity. The courts have held that the phrase 'in need thereof' as recited in independent claims 23 and 33 is meaningful, and that 'the claims' recitation of a patient or a human 'in need' gives life and meaning to the preambles' statement of purpose." *Jansen v. RexallSundown, Inc.* 342 F.3d 1329, 1333 (Fed. Cir. 2003). Since the cited claims do not teach or suggest treating obesity, the intent to treat human subjects in need of treatment for obesity, or the use of an amount effective to treat obesity, a skilled artisan would have no expectation of success for the claimed invention in view of the cited claims. In this regard, "[r]ejections on obviousness grounds cannot be sustained by mere conclusory statements;
instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR,* 127 S.Ct. at 1741 (quoting *In re Kahn* 441 F.3d 977, 988 (Fed. Cir. 2006). The prior art must still suggest a predictable outcome to establish a *prima facie* case of obviousness. See, e.g., *Takeda Chemical Industries, LM v. Alphapharm Pry., Ltd.* 492 F.3d 1350, 83 U.S.P.Q.2d 1169 (Fed. Cir. 2007).

(d) The Office's reliance on inherency in the context of anticipation in the rejection(s) is contrary to the law. Anticipation based on inherency is appropriate only when the prior art relied upon necessarily includes all of the elements of the claims in question and is the natural result of following the instructions or examples of the prior art. See, *Atofina v. GreatLakes Chemical Corp.,* 441 F.3d 991, 78 USPQ2d 1417, 1424 (Fed. Cir. 2006); *SmithKline Beecham Corp. v. Apotex Corp.,* 403 F.3d 1331, 1334, 74 USPQ2d 1398, 1407 (Fed. Cir. 2005) (citing *Schering Corp. v. Geneva Pharms., Inc.,* 339 F.

3d 1373, 1377, 67 USPQ2d 1664, 1667 (Fed. Cir. 2003)). The Court in *Schering* relied in part on the decision *In re Cruciferous Sprouts Litigation,* 301 F.3 d 1343, 1351, 64 USPQ2d 1202, 1206 (Fed. Cir. 2002) wherein it was noted that to demonstrate inherency, it was necessary to show that the prior art necessarily, always functions in accordance with the claims addressed. The requirement that the teaching of a reference always, under any circumstances, necessarily satisfies the recitation of the claims to make out a case of inherent anticipation was reaffirmed by the Federal Circuit in *Abbott Laboratories v. Baxter Pharmaceutical Products, Inc.,* 471 F.3d 1363, 1368 (Fed. Cir. 2006). It is well settled that a determination of inherency cannot be established by probabilities or possibilities, but that it is incumbent upon the Examiner to establish the inevitability of the inherency which is propounded. *In re Oelrich,* 666 F.2d 578, 581,212 USPQ 323,326 (CCPA 1981); *In re Wilding,* 535 F.2d 631, 635-36, 190 USPQ 59, 63-64 (CCPA 1976). Tsanev discloses that 80-90% of diabetic patients are obese, which falls short of the 100% (i.e., always, under any circumstances) criterion required by the present claims and required by the law. Accordingly, claims 34 and 35 of Gaeta support neither *prima facie* obviousness nor anticipation with regard to the claimed invention.

(e) The Office improperly asserts that the prior method necessarily includes all of the elements of the instant claims as evidenced by Thompson *et al.* (*Diabetes* 46: Suppl. 1, page 30A, 0116, 02 May 1997) (Thompson 1997). Appellants had filed a declaration under 37 C.F.R. § 1.131 in the response to Office Action filed December 2, 2002, which demonstrates that the current application antedates Thompson 1997 and was inventors' own work. Accordingly, Thompson 1997 is unavailable as prior art against the current application. More particularly, Thompson 1997 cannot be used as evidence of an alleged inherency because the present invention antedates Thompson 1997. The Office appears to require Thompson 1997 in order to demonstrate a nexus between administration of an amylin or agonist therefore and treatment for obesity. However, Appellant's invention was made prior to Thompson 1997, which is not available to supply the necessary connection between amylin or agonist thereof and treatment for obesity. Thus, the Office has failed to provide evidence or argument with any rational underpinning that the current claims are obvious in view of Gaeta as evidenced by Tsanev. Whatever else is taught by Gaeta and Tsanev, the references do not teach or suggest a method of treating obesity in a subject in need of treatment thereof.

The Office submits the following **rebuttal** to Appellants' arguments on both the rejections over Gaeta *et al.* ('411):

Contrary to Appellants' assertion, the prior art method necessarily includes *all* of the elements of the instant claims. As set forth previously, the '411 patent's patients seen by a medical practitioner, i.e., humans having diabetes mellitus, were administered with a therapeutically effective amount of the amylin agonist species recited in claim 19 of the '411 patent, ^{25,28,29}Pro-human amylin (i.e., pramlintide), the same amylin agonist or amylin agonist analogue species used by Appellants in Example 1 of the instant application. The method of treatment claimed in claims 34 and 35 of the '411 patent includes administering to such a patient with diabetes mellitus a therapeutically effective amount of the amylin agonist of claim 19 of the '411 patent, ^{25,28,29}Pro-human amylin (pramlintide). The portion of the disclosure of the '411 patent at second paragraph under 'Summary of the Invention' supporting the limitations 'diabetes mellitus' and 'administration of .... an amylin agonist analogue' include insulin-requiring diabetes mellitus and administration of an amylin agonist analogue alone (i.e., obesity relief agent consisting of or composition not in conjunction with another obesity relief agent) or with insulin or a glucagon, i.e., not in conjunction with another obesity relief agent. The portion of the disclosure of the '411 patent at lines 53-59 in column 8 supporting the limitation 'therapeutically effective amount' of the amylin agonist includes the dosage units of 0.1 to 5 mg or 0.5 to 1.0 mg of the amylin agonist. The amount effective to treat obesity, inhibit weight gain, or induce weight loss) encompassed in the instant claims as described in the instant application of about 0.01 milligrams to about 5 milligrams per day, or 300 micrograms per dose, falls within the range disclosed in the '411 patent. Given the art-known prevalence of intrinsic obesity in as many as 80% to 90% of diabetic patients as disclosed by Tsanev, 80-90% of the human diabetic patients used in the method disclosed in the '411 patent qualified as human patients in need of treatment for obesity. Therefore, the method of the '411 patent comprising or consisting of the administration of 0.1 to 5 mg, or 0.5 to 1.0 mg of the amylin agonist, ^{25,28,29}Pro-human amylin alone or in conjunction with insulin or glucagon, to 80-90% of the human diabetic patient species anticipates the instant claims. Given that the method step of the '411 patent and the instant claims are the *same*, the amylin agonist analogue pramlintide used and its amount administered are the *same*, and the human diabetic patient species used are the *same* (80-90% of whom are known to be obese), the method of the '411 patent is expected to necessarily bring about

the obesity-treating effect, weight gain-inhibiting effect, or weight loss-inducing effect in the intrinsically obese diabetic patient administered with a therapeutically effective amount of the pramlintide as claimed in the instant invention. Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the disclosure of Gaeta *et al.* ('411), Gaeta's ('411) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the obesity-treating effect, weight gain-inhibiting effect, or weight loss-inducing effect.

That the determination of inherency in the instant case is not established by probabilities or possibilities is further evidenced by the teachings of Thompson *et al.* (*Diabetes* 46: Suppl. 1, page 30A, 0116, 02 May 1997) (Thompson *et al.* May, 1997). The reference of Thompson *et al.* is cited solely to rebut Appellants' arguments by showing that the missing inherent matter is necessarily present in the method thing described in the prior art reference of '411 patent. Thompson *et al.* (May, 1997) showed that a method of subcutaneous administration of pramlintide, i.e., $^{25, 28, 29}$pro-h-amylin, an analog of human amylin, i.e., the same amylin agonist used in Example 1 of the instant invention, to patients with type II diabetes requiring insulin, at a dose 60 micrograms QID (i.e., four times a day) or TID (i.e., three times a day) not only improved glycemic control in these patients, ***but also decreased body weight concurrently*** (see abstract). Therefore, the method of the '411 patent necessarily served as a method of treating obesity. With regard Appellants' statement that Thompson (1997) cannot be used as evidence of an alleged inherency because the present invention antedates Thompson 1997, it should be noted that the critical date of extrinsic evidence need *not* antedate the filing date of the instant application. See MPEP § 2124.

It is a commonly known fact in the art that type II diabetic patients (80-90% of whom are known to be obese) are 'in need of' obesity. Appellants themselves characterize Type 2 diabetic subjects taking insulin as a particularly difficult to treat ***obese*** subject population. See first full paragraph of page 25 of Appellants' after-final amendment filed 05/12/08. With regard to Appellants' statement that Tsanev's disclosure that 80-90% of diabetic patients are obese falls short of the 100% (i.e., always, under any circumstances), the following must be noted. 'A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus'. The species in that case will anticipate the genus. *In re Slayter*, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); *In re Gosteli*, 872 F.2d 1008,

10 USPQ2d 1614 (Fed. Cir. 1989). A genus does not always anticipate a claim to a species within the genus. However, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. In *In re Sivaramakrishnan*, 673 F.2d 1383, 213 USPQ 441 (CCPA 1982), the claims were directed to polycarbonate containing cadmium laurate as an additive. The court upheld the Board's finding that a reference specifically naming cadmium laurate as an additive amongst a list of many suitable salts in polycarbonate resin anticipated the claims. The applicant had argued that cadmium laurate was only disclosed as representative of the salts and was expected to have the same properties as the other salts listed while, as shown in the application, *cadmium laurate had unexpected properties*. The court held that it *did not matter that the salt was not disclosed as being preferred, the reference still anticipated the claims* and because the claim was anticipated, *the unexpected properties were immaterial*. Although the instant claims are method claims, in the instant application, the prior art disclosure of a method comprising or consisting of the administration of 0.1 to 5 mg, or 0.5 to 1.0 mg of the amylin agonist, ^{25,28,29}Pro-human amylin alone or in conjunction with insulin or glucagon, to 80-90% of the human diabetic patient species anticipates the instantly claimed method. The claims are anticipated because the administered ^{25,28,29}Pro-human amylin also inherently exerted obesity-relieving properties in said method. See also *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.). In the instant application, the obesity-relief, weight gain inhibition, or weight loss-induction is an intrinsic property inseparable from the administered pramlintide. The two structurally identical pramlintide compounds administered in the two methods (i.e., the prior art method and the instant method) cannot have mutually exclusive properties. As set forth above, this is evidenced by the teachings of Thompson *et al.* (1997) who showed that a method of subcutaneous administration of pramlintide, i.e., $^{25, 28, 29}$pro-h-amylin, an analog of human amylin, i.e., an amylin agonist, to patients with type II diabetes requiring insulin, at a dose 60 micrograms QID or TID not only improved glycaemic control in these patients, but ***also decreased body weight concurrently***

(see abstract). Therefore, the prior art method necessarily served as a method of treating obesity. The same two methods (i.e., the prior art method and the instant method) cannot have mutually exclusive results.

In the instant application, it is important to note that the *human patient species used in Example 1 of the instant specification for treatment of obesity via administration of pramlintide are indeed type II diabetic human patients*. Thus, the prior art disclosure is commensurate in scope with the instant disclosure with regard to the type 2 diabetic human subject population used, the pramlintide compound administered, and the amount and frequency of pramlintide administered to the type 2 diabetic human patient species.

In the instant case, the claims are drawn to a method that uses generic human subjects. The method is not limited to treating obesity in non-diabetic obese human patients, but encompasses treating obesity in type II diabetic human patients, 80-90% of whom are known in the art to have intrinsic obesity. In other words, treatment of obesity in type II diabetic human patients is just one of the species or embodiments encompassed within the scope of the genus of human subjects in need of such treatment. That 10-20% of prior art diabetic patients, to whom pramlintide is administered, are not expected to be obese is not relevant since an anticipatory reference has to teach only one species or one embodiment encompassed by the scope of the genus claims. Under the principles of inherency, a reference may be directed to an entirely different problem than the one addressed by the inventor, or may be from an entirely different field of endeavor than that of the claimed invention, yet the reference is still anticipatory if it explicitly or inherently discloses every limitation recited in the claims. See *State Contracting & Eng'g Corp. v. Condotte America, Inc.*, 346 F.3d 1057, 1068, 68 USPQ2d 1481, 1488 (Fed. Cir. 2003). Appellants appear to be arguing that in order to be anticipatory, a prior patent has to teach each and every species or embodiment encompassed within the scope of the instant claims. The argument is not persuasive.

To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of

record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). See MPEP 2124. Tsanev's extrinsic evidence makes clear that the missing descriptive matter, i.e., prevalence of obesity in at least one of Gaeta's ('411) insulin-requiring diabetic subjects administered with ^{25,28,29}Pro-human amylin, is necessarily present in the thing described by Gaeta *et al.* ('411). The method of Gaeta *et al.* ('411) clearly anticipates the claimed method of the instant invention, because Gaeta *et al.* ('411) taught the very step of the instantly claimed method in the very same diabetic human patient species. The alleged failure of Gaeta *et al.* ('411) to expressly mention treatment of obesity as a goal is irrelevant. To the extent the method embodiment in the claimed invention achieves treatment of obesity, so does the method of Gaeta *et al.* ('411). Where the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results. See *Mehl/Biophile International Corp. v. Milgraum*, U.S. Court of Appeals Federal Court, 52 USPQ2d 1303 and 1306, 192 F3d 1362, 1999 citing *W.L. Gore & Assocs. v. Garlack, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983).

For the detailed reasons delineated above, both the rejections of record over the '411 patent should be sustained.

(VII) In response to the rejection of claims 23, 24, 27, 29, 33, 34, 37 and 38 made in paragraph 29 of the Office Action mailed 02/11/08 and maintained in paragraph 17 of the Office Action mailed 05/28/08 under 35 U.S.C § 102(e)(2) over Beumont *et al.* ('008) as evidenced by Tsanev, Appellants reiterate the same **arguments** that they have presented on the obviousness double patenting rejection over US patent 5,321,008. See the paragraph immediately below for Appellants' arguments on both the rejections and the Office's response. Appellants also state that they reiterate the arguments submitted over the obviousness double patenting rejection over the '411 patent. Appellants are referred to the Office's response provided in the immediate paragraph above for the Office's response to Appellants' arguments on the rejections over the '411 patent.

(VIII) In response to the rejection of claims 23 and 33 made in paragraph 22 of the Office Action mailed 02/11/08 and maintained in paragraph 12 of the Office Action mailed 05/2/08 under the judicially created doctrine of obviousness-type double patenting over claims 11 and 13 of Beumont *et al.* ('008) as evidenced by Tsanev, Appellants submit the following **arguments**.

(a) The references individually or in combination provide no guidance concerning the identification of or intent to treat a subject in need of treatment for obesity. Claim 11 of Beaumont ('008) is directed to a method of treating diabetes mellitus in an insulin-requiring mammal (human) comprising administering a therapeutically effective amount of calcitonin. Claim 13 of Beaumont ('008) is directed to a method of treating type II diabetes mellitus comprising the step of administering a therapeutically effective amount of insulin and calcitonin to achieve improved glycemic control. Beaumont is silent with regard to the treatment of obesity.

(b) In view of the similarity of the current rejection to the non-statutory double patenting rejection over Gaeta ('411) discussed above, arguments provided above in relation to that rejection are reiterated herein. Arguments provided for the double patenting rejection over Gaeta ('411) are hereby reiterated.

Appellants are referred to sections V and VI above for the Office's detailed **response**.

'To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). See MPEP 2124. Tsanev's extrinsic evidence makes clear that the missing descriptive matter, i.e., prevalence of obesity in 80 to 90% of Beumont's ('008) insulin-requiring diabetic subjects administered with

calcitonin, is necessarily present in the method thing described by Beumont *et al.* ('008). The method of Beumont *et al.* ('008) clearly anticipates the claimed method of the instant invention, because Beumont *et al.* ('008) taught the very step of the instantly claimed method in the very same diabetic human patient. Given that calcitonin is an art-known amylin agonist (see lines 45-47 in column 7 of US patent 5,739,106; claims 3 and 10 of US 5,175,145; and first full paragraph on page 9 of the instant specification), it necessarily has intrinsic obesity-relieving effects. The alleged failure of Beumont *et al.* ('008) to expressly mention treatment of obesity as a goal is irrelevant. To the extent the method embodiment in the claimed invention achieves treatment of obesity, so does the method of Beumont *et al.* ('008). Where the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results. See *Mehl/Biophile International Corp. v. Milgraum*, U.S. Court of Appeals Federal Court, 52 USPQ2d 1303 and 1306, 192 F3d 1362, 1999 citing *W.L. Gore & Assocs. v. Garlack, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983).

For the reasons delineated above, both the rejections over the '008 patent should be sustained.

(11) Related Proceedings Appendix

No decision rendered by a court or the Board is identified by the Examiner in the Related Appeals and Interferences section of this examiner's answer.

Respectfully submitted

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